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CONTENTS

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Jubilee Volume

dedicated to

KAROLINSKA INSTITUTET

on its One Hundred and Fiftieth Anniversary

by

THE TWO PEDIATRIC CLINICS OF
THE INSTITUTE

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From the Pediatric Clinic of Karolinska Institutet at Karolinska sjukhuset, Stockholm, Sweden

The Birth of a Medical School

by ARVID WALLGREN

Modern Sweden may be called a prosperous country, not only economically but also as regards the people's state of health. During previous centuries the conditions were quite different. Sweden was then very poor under the economic stress and strain of repeated warfare, the sanitary conditions were primitive or lacking, and the morbidity and mortality rates were very high. The very few physicians were mostly trained abroad. The medical faculties at the Universities of Uppsala and Lund each had only two professors, and hospitals for the practical instruction of medical students were few or non-existent. The care of war-wounded soldiers and of the civilian population was principally entrusted to barber-surgeons ("fältskär") and quacks. The profession of barber-surgeon was a handicraft, usually combined with haircutting and shaving. Those wishing to become barber-surgeons were trained by master barber-surgeons, much in the same way as the training of tailors, carpenters and shoemakers was in the hands of master craftsmen. They were forbidden to treat anything but common external disorders, fractures and wounds; the treatment of epidemic and internal diseases was the sole privilege of properly trained physicians.

A Collegium medicum was formed in 1663 of the four practising physicians in Stockholm for the purpose of supervising the barber-surgeons, pharmacists and midwives, as well as examining the professional qualifications of physicians wishing to practise in Stockholm. This Collegium was the forerunner of the State Board of Health. In 1688 it was charged with the duty of examining all physicians educated in Sweden or abroad who wanted to obtain posts as provincial or city physicians. A Surgical Society was in turn organized by the eighteen master barber-surgeons in Stockholm; it examined candidates wishing to become barber-surgeons.

At the end of the seventeenth and the beginning of the eighteenth century demonstrations in anatomy were given by members of the Collegium medicum for barber-surgeons and physicians. For some years members of the Surgical Society competed by giving lectures in anatomy and surgery to barber-surgeon apprentices. In 1756 a professor of anatomy and surgery was appointed by the government to the Collegium medicum and entrusted with the duty of teaching these two subjects to the barber-surgeon apprentices. However, the pupils also included many

physicians and medical students from Uppsala who were obliged to serve from six to twelve months at Serafimerlasarettet in Stockholm before they could qualify for official positions as physicians. Serafimerlasarettet was an independent hospital, inaugurated in 1752. Lectures and demonstrations were given by the head surgeon and the head physician of the hospital.

Serafimerlasarettet had a few beds for obstetrical cases for teaching purposes. A separate lying-in hospital was built twenty years later in Stockholm (Allmänna Barnbördshuset). A professor of obstetrics was appointed in 1761 and he taught the discipline to midwives as well as to physicians and barber-surgeons.

A professorial chair of biology and pharmacy was created in 1761 for the instruction of pharmacists. This professorship was changed, in 1790, to one of medicine and pharmacy. Lectures were given to barber-surgeons and physicians in epidemic diseases and disorders prevalent in the army and the navy, besides the instruction of pharmacy pupils.

The three professors in anatomy and surgery, obstetrics, and medicine and pharmacy were in the service of the Collegium medicum, which in 1797 assumed all the responsibility for the entire medical profession in Sweden, including supervision of the barber-surgeons. The Surgical Society was then discontinued. At the turn of the eighteenth century the three professors organized a School of Surgery. Sweden was now at war and the sanitary conditions in the armed forces deteriorated as before and the troops sustained heavy losses from diseases and neglected wounds. The need became urgent for increased numbers of trained physicians and barber-surgeons.

At last the parliament decided in 1810 to create a "Medico-Surgical Institute" in Stockholm, for the training of barber-surgeons, and of army and navy physicians. A military hospital was to be built in order to facilitate the training. The nucleus of the Institute was formed of the three independent professors of the Collegium medicum and two new professors of theoretical and of practical medicine for the training of barber-surgeons, midwives and pharmacists. Together they constituted the whole faculty of the Institute.

The training of barber-surgeons as a craft was now replaced by the theoretical and scientific teaching and practical and clinical hospital training of surgeons. However, a strict separation was kept between medicine and surgery as teaching subjects: medicine was taught at the Universities, and surgery at the Medico-Surgical Institute. The teaching was conducted by the head surgeon at the military hospital which was inaugurated in 1811 with 200 beds. In addition the teaching proceeded as before at Serafimerlasarettet, which at this time had 100 beds.

The responsibility of the Institute as a medical school was broadened in 1821: to prepare physicians for official civilian as well as military positions by giving the principally theoretically educated, university Dr. Med. the required practical training in medicine and surgery. The teaching at the military hospital was discontinued but went on at Serafimerlasarettet. This hospital was kept as an independent hospital until 1833 when it was incorporated with the Institute as its own

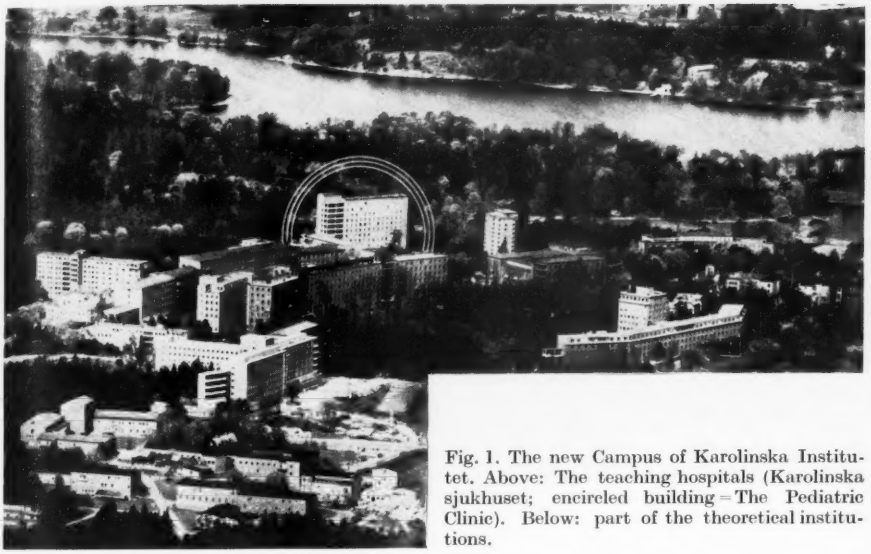

Fig. 1. The new Campus of Karolinska Institutet. Above: The teaching hospitals (Karolinska sjukhuset; encircled building = The Pediatric Clinic). Below: part of the theoretical institutions.

teaching hospital. The head of the medical department became professor of internal medicine, and the head of the surgical department came to be professor of surgery at the Institute.

The Medico-Surgical Institute was in 1816 called Karolinska Institutet in honor of Charles XIII. At this time six professors were engaged there, in anatomy, biology, chemistry, theoretical and practical medicine, including physiology and pathology, obstetrics, and theoretical and practical surgery, including special pathology.

At first the students were admitted after having passed an oral examination conducted by professors of the Institute. In 1822 the Institute required that the students should have passed the same preparatory medico-philosophical examination (zoology, botany, physics and chemistry) as the students at the Uppsala and Lund Universities, and thus be evenly matched with the medical students studying at the medical faculties of these two universities. Students have always been accepted in limited numbers. One hundred students have been admitted annually after the doubling of the chairs of the clinical subjects at that time considered most important, namely medicine, surgery, obstetrics and pediatrics.

Those who had passed the master of surgery examination at Karolinska Institutet could practise medicine, but were not qualified to obtain official appointments as physicians. This was the prerogative of the Dr. Med. of the universities after having passed the master of surgery examination at the Institute.

This restriction of the Institute's as well as of the universities' task of producing qualified physicians was considered derogatory from their independence as medical teaching centers, and gave rise to heated discussions and decade-long conflicts. The Institute was as anxious to become a com-

plete and independent medical school, as the universities were anxious to keep the Institute at its then low level or to abolish it altogether. The principal spokesman for the Institute was the famous chemist, Professor J. Berzelius, while the universities had an eloquent advocate in Professor I. Hwasser.

In the meantime "the professors of Karolinska Institutet have quietly and purposefully built the proud edifice, brick by brick, and founded it on scientific research into a modern medical school" (Lennmalm). The number of teachers increased gradually with the expansion of its curriculum: state medicine (1841), pediatrics (1845), pathological anatomy (1853), syphilology (1856), psychiatry (1861), physiology (1873), neurology (1887), opthalmology (1891), oto-laryngology (1901) and roentgenology (1908).

Despite the opposition to the Institute by the universities, which abated slowly during the last half of the nineteenth century, the Institute assumed increased responsibility for the education of physicians. The government decided in 1853 that all Swedish medical students should be obliged to serve for at least one year at Serafimerlasarettet and at the Lying-in Hospital in Stockholm before they were admitted to take their state medical examination (licentiate of medicine). In 1861 the Institute was granted the same right as the universities to teach and examine the students for the licentiate of medicine examination. The first degree of the medical examination (candidate of medicine) remained exclusively in the hands of the universities until 1873, when the Institute obtained equal rights with the universities as regards examinations. A certain portion of the teaching remained for many decades the prerogative of the universities and another portion that of the Institute. The students who had passed their licentiate of medicine examination could prepare and defend their doctoral thesis at the Institute, but it was not before in 1906 that the Institute was granted the right to confer the Dr. Med. degree.

During the past fifty years the evolution of Karolinska Institutet has been very rapid with regard to the number of teachers, laboratories and clinics. It has developed into Sweden's most prominent teaching and research center in medicine. Since 1901 the Institute has been entrusted with the honourable but difficult task of conferring annually the Nobel Prize in Physiology and Medicine. This involves great responsibility and implies the duty to follow carefully the progress of current medical research in the whole world.

Twenty years ago the theoretical institutions of the Instistute moved from their old-fashioned premises into modern buildings on the new campus in a suburb of Stockholm. A little later the construction of a teaching hospital, Karolinska Sjukhuset, started with the inauguration of new medical, surgical, obstetrical, oto-laryngological and opthalmologic clinics, and radiodiagnostic and radiotherapeutic departments. The dermato-venereologic, pediatric, rheumatologic and thoracic (including thoracic surgery) clinics were opened in the 1950s, and during the 1960s an alcoholics clinic and neurological, neurosurgical and orthopedic departments will be built. Serafimerlasarettet is still functioning, with medical, surgical and radiodiagnostic departments, and with the neurological and neurosurgical clinics

which will be moved to Karolinska Sjukhuset. The other clinics of Serafimerlasarettet, together with the pediatric clinic at the Crown Princess Lovisa Hospital will be replaced by new departments at the Sabbatsberg Hospital, where already one of the two obstetrical and one of the two pathological departments are housed. In all Karolinska Institutet will have about 25 theoretical institutions and more than 30 clinics. At present 87 academic teachers are on the Institute's permanent staff, in addition to about 250 appointed honorary assistant professors (docents).

The library of the Institute has the largest collection of medical books in Sweden and functions as a central library for the whole country. It contains about 235,000 volumes and the number of current medical journals is about 1300.

This brief account of the first 150 years of the evolution of Karolinska Institutet may be closed with a sentence from Professor F. Lennmalm's history of the Institute written for its centenary in 1910:

"It is our hope that future staff of Karolinska Institutet will be worthy of their predecessors in carrying out their duties, which their position imposes on them, for their country, medical science and mankind."

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Pediatric Clinic
Karolinska sjukhuset
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From the Pediatric Clinic of Karolinska Institutet at Karolinska sjukhuset, Stockholm, Sweden

The Pediatric Clinics and the Pediatric Teaching at Karolinska Institutet

by ARVID WALLGREN

In Sweden, as elsewhere, the teaching of pediatrics in former days belonged to the duties of the professor of internal medicine. The extent to which the physiology and pathology of childhood was taught to the students depended on the intern's interest in these subjects. In the middle of the 18th century pediatrics in Sweden lived through a golden age, thanks to the famous Dr. Nils Rosén von Rosenstein, who was professor of medicine at the University of Uppsala. His special interest was childhood and his lectures were published in the popular almanac which appeared annually. It was distributed everywhere in the country and was studied by all who had learned to read. In 1793 the lectures were collected and published in a book called "Information on Children's Diseases and their Treatment". It appeared in many editions and was used for years as a textbook by students, not only in Sweden but (translated into 7 foreign languages) in several other countries in Europe.

Pediatric teaching at this time, if it was given at all, dealt with morbid conditions in childhood, illustrated by reports of typical cases from the professor's own private practice. In Sweden there were no hospital beds for sick children nor were there any pediatric out-patient departments. The only type of institution that existed for children was a kind of asylum in which orphans were admitted. These asylums, of which the largest was the State General Orphanage (Allmänna Barnhuset) in Stockholm, were not used for medical teaching purposes at this time.

After the retirement of Dr. Rosén from the chair of medicine at Uppsala University, there is very little information about pediatric teaching, and the interest of the professors of internal medicine in this part of their duties was probably rather halfhearted. This applies to the Universities of Uppsala and Lund, the only medical schools in Sweden until 1810, when Karolinska Institutet in Stockholm was founded. That there really existed an understanding of the importance of teaching child health and child care to future physicians is shown by one of the regulations of the Institute in 1822. This stated that students of medicine had to attend ward rounds and assist in giving smallpox vaccinations at the State General Orphanage for two months before they could pass their master of surgery examination. An active physician at the Orphanage who was interested in teaching would have an

excellent opportunity to give the students a quite substantial amount of pediatric knowledge and training. Unfortunately this did not happen, which is understandable, as the position of orphanage physician was very much a spare-time job with a meagre salary and very limited authority. The two months' training at the State Orphanage merely consisted of assisting with the smallpox vaccinations.

In 1838 far-seeing members of the Board of the State Orphanage and of the Faculty of Karolinska Institutet who clearly understood the need for pediatric training of future physicians put in a plea for such a program to the government. This appeal did not meet with any success, and subsequent proposals of the same kind made by the Faculty during the next few years suffered the same fate. In 1842 this plea again was raised, supported by very strong arguments in its favour. The Faculty this time recommended the appointment of a professor to teach clinical pediatrics at the State Orphanage. At last the government approved and after prolonged discussions, the parliament of 1844 granted the necessary funds for a professor of pediatrics and for the establishment of pediatric teaching at the State Orphanage.

The acting physician of the State Orphanage was scarcely qualified for the post of professor of pediatrics. In Stockholm, however, there was a physician, Fredrik Theodor Berg, who by accident had come to be interested in pediatrics. In 1838 he had been asked by a member of the Board of the State Orphanage to study critically a draft for the construction of a hospital for sick children at the State Orphanage. Later, in 1839, when he made a study tour abroad, he was commissioned by the Board of the Orphanage to concentrate his attention on children's hospitals and the methods of child care in the foreign countries he visited. A couple of months after he left Sweden, the Board appointed him "clinical physician" at the State Orphanage with the special duty of teaching medical students. After his return in 1841, Dr. Berg took up his new post as "clinical physician". He was impressed by his recent experiences in modern institutions for children on the continent, and was struck by the unsatisfactory sanitary and organisational conditions at the State Orphanage. He declared that it was impossible to teach until comprehensive reorganisation of the Orphanage had been accomplished. This criticism gave rise to severe conflicts between Dr. Berg and the Board, a controversy that lasted for several years. A thorough re-organisation was not made until 1851.

In 1845 Berg was appointed professor of pediatrics at Karolinska Institutet by the government, and the State Orphanage thus became the first pediatric clinic in Sweden. Dr. Berg did not lack clinical material for his teaching. The Orphanage had beds for 100 older children and a still greater number of beds for infants, many of them sick. In the children's hospitals of other European nations, teaching in pediatrics had been given to medical students, but this teaching was voluntary and was not followed by any examination. At the Institute this subject was, from the beginning, separated from internal medicine, and it had its own representative on the Faculty. Instruction as well as examination in pediatrics became compulsory for future physicians.

In his formal teaching, Berg gave twice

Fig. 1. The Crown Princess Lovisa's Children's Hospital (Kronprinsessan Lovisas Barnsjukhus).

weekly systematic lectures on health and disease in childhood. In addition, every weekday the students received practical training in the diagnosis and treatment of common diseases of infants and nursing mothers. With regard to older children, Berg had to content himself with theoretical teaching on account of poor facilities and lack of assistance. He had only one assistant who was appointed by the Institute. The former physician at the Orphanage, chosen by its Board, had nothing to do with teaching and soon retired. Instruction in pediatrics, which started on May 2, 1845, was conducted in the form of a four months' course and was repeated twice annually. The number of students was restricted to 25 each term.

Dr. Berg's unpleasant controversy with the Board of the State Orphanage regarding the necessary re-organization of the Orphanage continued and at last caused Berg to resign in 1846, from his post as head physician of the Orphanage. Three years later the Board granted Dr. Berg leave of absence from this post and appointed his assistant, Dr. Hjalmar Abelin, as his deputy. Dr. Abelin became permanent head physician in 1851, when Berg's resignation was at last accepted. Berg, however, continued his teaching at the Orphanage as professor of pediatrics at Karolinska Institutet until he took leave of absence to become deputy Councillor at the State Board of Health in 1854. After Dr. Berg's resignation in 1858 Dr.

Abelin became professor of pediatrics. In the meantime Berg, in 1851, had established an out-patient department for sick children at the State Orphanage, an event which was of great importance and value for the teaching of pediatrics.

Gradually it became evident that the teaching duties could not be handled by the professor alone and a lecturer in pediatrics, Dr. Adolf Kjellberg, was therefore appointed in 1861. Eighteen years later, in 1879, this lectureship was transformed into the post of associate professor of pediatrics at Karolinska Institutet. In the beginning, Dr. Kjellberg's teaching was in connection with post-mortem examinations, but after a few years the responsibility of instruction was evenly divided between the two professors.

The same year that Dr. Kjellberg became lecturer in pediatrics, he was appointed head physician of the Crown Princess Lovisa Children's Hospital. This hospital was founded in 1854 on private initiative and was operated by private means. It was the first hospital for sick children in Sweden. Instrumental in its foundation were members of the Faculty of Karolinska Institutet, especially the professor of internal medicine, Magnus Huss. The hospital could admit 40 sick children aged 2–8 years, but was later enlarged to contain 60 beds. After the retirement of Abelin in 1882, Kjellberg became professor of pediatrics and head of the State Orphanage, but also remained head physician of the Lovisa Hospital. On his own initiative he started voluntary teaching in pediatrics one hour twice weekly at the Lovisa Hospital for medical students following the curriculum at the State Orphanage. A few years later, a formal agreement between the Institute and the Board of the Lovisa Hospital was made, by which the latter hospital became an independent clinic for pediatric teaching with the associate professor as head of the hospital. From then on, the medical students were divided into two equal groups, one of which was assigned to the professor at the State Orphanage and the other to the professor at the Lovisa Hospital. Kjellberg now retired as head physician of the Lovisa Hospital and kept only his post as head of the State Orphanage. Dr. Oscar Medin became his sucessor as associate professor and head of the Lovisa Hospital. When Kjellberg died in 1884, Medin succeeded him as professor and head of the State Orphanage. Dr. Jonas Waern was then appointed associate professor and head of the Lovisa Hospital. In 1909, the associate professorship was transformed into a second full professorial chair of pediatrics.

By and by the two pediatric clinics with their out-patient departments became too small to meet the needs of sick children and to fulfil their mission as pediatric teaching and training units. A new building with 138 beds, including a separate surgical department with its own head, was constructed in 1899 for the Crown Princess Lovisa Children's Hospital, at the present site of the hospital on Polhemsgatan. During the terms of Adolf Lichtenstein (1931–1949) and Curt Gyllenswärd (1950–) as professors of pediatrics at the Lovisa Hospital, this hospital has undergone several reconstructions and extensions, and the number of beds, including surgical wards at the Sachs Children's Hospital, has gradually been increased to 180. In 1950, the facilities of the surgical

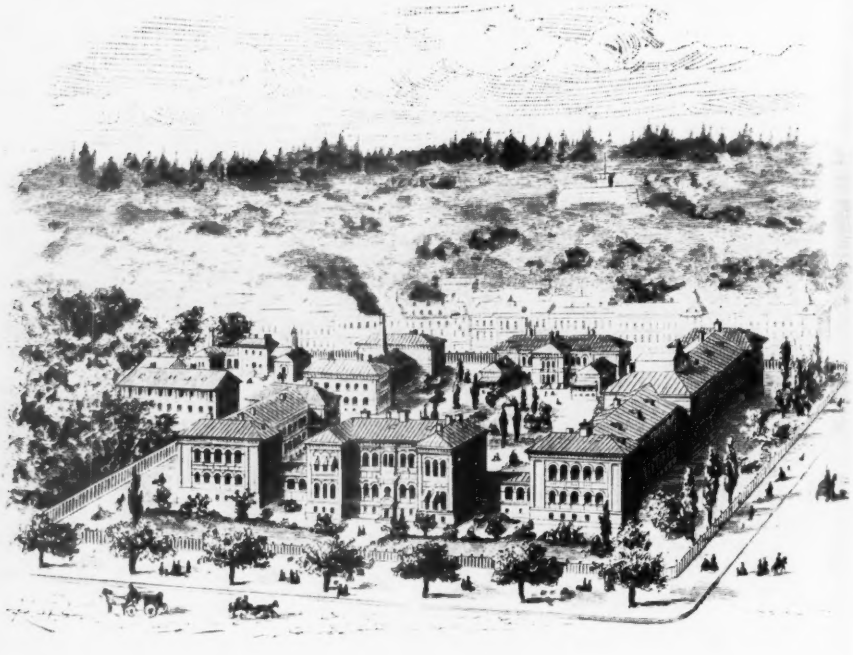

Fig. 2. The State Orphanage (Allmänna Barnhuset) inaugurated in 1885. The small separate building in the background is the hospital of the Orphanage. In 1931 the Orphanage was sold to the City of Stockholm and transformed into Norrtull's Hospital.

department of the hospital were included in the teaching of students and in 1953, a department of child psychiatry was established with a head physician. Five years later this post was transformed into a chair of child psychiatry at Karolinska Institutet. In 1948 it was decided, in principle, that the Lovisa Clinic should move to the Sabbatsberg General Hospital. After prolonged negotiations, this project took definite form and one can now look forward to the construction of a new clinic at Sabbatsberg Hospital within the next few years. This clinic will be provided with the same in- and out-patient departments, laboratories and equipment as the new clinic at the Karolinska Hospital (Karolinska Sjukhuset) (see below).

In 1885, while Medin was professor of pediatrics and head of the State General Orphanage, this institution was moved to new premises at Norrtullsgatan. The new Orphanage included a hospital building for the Orphanage's own sick children. Medin retired in 1912 and was succeeded by Dr. Isak Jundell. During his term a very important change occurred with regard to the organization of the Orphanage. In 1917, Sweden enacted new legislation concerning illegitimate children, which le-

prived orphanages of some of their original responsibilities for the care and education of destitute children. A re-orientation of their field of action had to be made and the orphans were to be placed elsewhere. In order to guarantee the training and teaching of medical students, the Faculty of Karolinska Institutet requested permission to admit up to 45 sick children from outside. In 1929, this was granted and after a while the number of beds was increased to 60 and finally to 75.

By the new law on the social welfare of children passed in 1924, it was strictly prohibited to admit healthy children into institutions for long-term collective care; these children were to be placed in private families as foster-children. Thus the State Orphanage lost its raison d'être, its policy had to be changed, and a re-organization became urgent. The buildings of the Orphanage was sold to the City of Stockholm in 1931 and the premises were partly transformed into a children's municipal hospital called the Norrtull Hospital with 75 beds. According to a agreement with the City of Stockholm, Norrtull Children's Hospital remained a teaching pediatric clinic with one of the professors of pediatrics at Karolinska Institutet as head physician, until a projected new children's department at Karolinska Sjukhuset was ready. This was calculated to take 10 years or until 1941. As a matter of fact, it was not until another 10 years had elapsed that the pediatric clinic was moved from Norrtull Hospital to its new premises at Karolinska Sjukhuset.

Karolinska Sjukhuset was originally planned to contain all the double clinics of Karolinska Institutet (there were two medical, surgical, obstetric and pediatric clinics). The Royal Committee in charge of the planning and organization of Karolinska Sjukhuset expressed doubts about the advisability of building two separate pediatric clinics with out-patient departments within the same area. They maintained that the patient material would be insufficient and that the training at the out-patient departments would suffer. Fortunately, due regard was paid to these misgivings when the definitive plan of Karolinska Sjukhuset was drawn up. The Royal Committee suggested that one pediatric department with 96 beds should be built in the first stage of construction of Karolinska Sjukhuset. When the question was discussed in the parliament of 1930, the government held, however, that because of the planned re-organization of the State Orphanage, the resolution for the construction of a pediatric department could not be passed at that time. In addition, it had been questioned whether two separate clinics and two professors of pediatrics were needed at Karolinska Institutet. The parliament therefore concluded that the decision regarding a pediatric department at Karolinska Sjukhuset should to be postponed.

As already mentioned, the re-organization of the State Orphanage was accomplished in 1930, and the question regarding the number of professors of pediatrics at the Institute was solved by the parliament in 1932. It was considered indispensable to retain two professors of pediatrics and two separate pediatric clinics.

Jundell retired in 1932 and was succeeded by Dr. Wilhelm Wernstedt, who had gone to Norrtull Hospital from the Lovisa Hospital, after having been appointed professor and head of the latter

hospital in 1921. The planning Committee of Karolinska Sjukhuset was instructed by the government in 1935 to produce a draft plan and an estimate of the construction cost for a pediatric department at the Hospital. This commission, however, was not carried out because the problem of the two chairs of pediatrics arose again in connection with the retirement of Wernstedt in 1937. In addition, no definite agreement had been reached regarding which of the two existing teaching hospitals for children, Norrtull or Lovisa, should be replaced by the planned department at Karolinska Sjukhuset. At last, in 1939, a new Royal Committee was formed with instructions to negotiate with the Boards of the two hospitals and to produce a draft decision about the future of the two pediatric clinics. In 1940, this Committee reached agreement in principle and gave a rough outline of a children's department at Karolinska Sjukhuset to replace the clinic at Norrtull Hospital. The Committee considered replacement of the Lovisa Hospital less urgent because funds had been set aside by the City of Stockholm for modernizing this hospital, which would make it suitable for use as a pediatric clinic for at least another 10 years. The Committee emphasized that, with regard to medical teaching, the most pressing of the hospital problems in Stockholm was that of the Norrtull Hospital. The City intended to close this hospital and therefore did not want to finance any improvements on the premises and the equipment. The draft plan of the new clinic at Karolinska Sjukhuset proposed 219 beds, of which 60 would be in the surgical and 20 in the psychiatric department. After the project to abolish one of the professorial chairs of pediatrics had again been rejected by parliament in 1942, the government charged the Planning Committee of Karolinska Sjukhuset to prepare definite plans and an estimate of costs according to the drafted plan.

The carrying out of the project was delayed, however, while the need for pediatric hospital beds rapidly increased, owing to the high birth rate of the early 1940s. Therefore on the proposal of Dr. Arvid Wallgren, who had been appointed professor of pediatrics at Karolinska Institutet in 1942, the Board of the City Hospitals decided to make a large-scale but provisional reconstruction of Norrtull Hospital. When this was completed in 1945, the number of beds rose to 150 and the hospital was provided with a department of child psychiatry. Norrtull Hospital now became much better qualified to serve as a pediatric teaching unit.

The definitive construction plan of the new clinic at Karolinska Sjukhuset was drawn up by the architect Sven Ahlbom, according to an outline made by Professor Lichtenstein of the Lovisa Clinic. In 1945 it was presented to the government by the Planning Committee. The program was accepted, and in 1946 the parliament allocated funds to carry out the project. In 1951, the department of pediatrics at Karolinska Sjukhuset was ready for use.

The department consists of a separate unit divided into three parts. The main ten-storey building is situated in the middle of the unit in an east–west direction, and contains principally wards. One three-storey wing to the south houses the out-patient departments, the ordinary and research laboratories and a roentgen diagnostic department. The three-storey north

Fig. 3. The Pediatric Clinic at Karolinska Sjukhuset.

wing contains a lecture theatre and other lecture rooms, a library, rooms for the heads of the clinic, residents and students, as well as a whole floor for surgery. The clinic has 212 beds for newborn babies and children up to 17 years of age. The department of child psychiatry with 13 beds is on the bottom floor of the main building and on the 2nd floor there are wards for infectious diseases with 21 beds. The 3rd and 4th floors constitute the department of surgery with 55 beds. The department of medicine has 26 beds for small children (5th floor), 26 beds for older boys (6th floor), 26 beds for older girls (7th floor) and 17 beds for infants including premature babies (9th floor). The 8th floor contains 19 mixed medical and surgical beds for private patients. On the 10th floor there are rooms for nursing mothers and the hospital kitchen.

The lecture theatre has 67 seats and may be enlarged to 100 seats by opening folding doors to a conference room located behind it. The lecture room is used for teaching student nurses. The clinic constitutes the only school for pediatric nursing in Sweden.

The department of pediatrics is a relatively independent unit with its own surgical, psychiatric and radiodiagnostic departments, with biochemical, hematological, cardiovascular, physiological, metabolic, neurological and allergological diag-

nostic and research laboratories. Only when bacteriological examinations and more complicated biochemical analyses are required does the clinic have to rely upon the central laboratories of Karolinska Sjukhuset.

There are special out-patient departments for surgery, diabetes, cerebral palsy, epilepsy, allergic and cardiovascular diseases. The out-patient department has a special research unit for the study of the longitudinal growth and development of healthy children, sponsored by the International Children's Center in Paris.

When compulsory teaching and training in pediatrics for medical students of Karolinska Institutet started in 1845, the teaching, as already mentioned, was given in the form of a 4-month course with 2 hours of lectures twice weekly. The course was repeated twice annually and only 25 students were accepted at the same time. In 1908, a new medical curriculum and training program was introduced in Sweden. The length of the pediatric course was reduced to 3 months, with 2 hours' teaching in the lecture room and the out-patient department and ward rounds 4 times a week. In addition to the 3-month course, every Swedish medical student had to serve as a clerk at the State Orphanage; unfortunately this clerical training stopped after a few years.

As regards teaching in child psychiatry, it may be mentioned that Jundell had made a plan for a child guidance clinic attached to the Norrtull Hospital. This project was carried out by Wernstedt, and a child psychologist was put in charge of the teaching. In this way, the first instruction in child psychology and psychiatry began at Karolinska Institutet. When Norrtull Hospital was reconstructed in 1945, the Board of the City Hospitals appointed a child psychiatrist to be in charge of a newly formed ward for children with mental disturbances. More regular lectures and demonstrations in child psychiatry were now given. Four years later, teaching in child psychology and psychiatry became compulsory at Karolinska Institutet. In the new children's department at Karolinska Sjukhuset, the head of the department of child psychiatry is charged with a considerable part of the pediatric curriculum and training. It is regrettable that so far there is no provision for an out-patient department for children with psychic disturbances. As already stated, the Lovisa Hospital was provided with a department of child psychiatry in 1953, and in 1958 the head of the department was appointed professor of child psychiatry.

There was no teaching in pediatric surgery until the middle of the 1940s, when a few lectures and demonstrations were given by the head of the surgical department of the Lovisa Hospital. In 1949, this teaching became compulsory and, at present, the heads of the surgical departments of the two pediatric clinics are responsible for the teaching and training of students in the common surgical diseases of childhood.

In 1948, each of the two pediatric clinics obtained a lecturer in pediatrics to take over some of the professor's teaching responsibilities. Gradually, new ideas regarding the teaching of pediatrics for future physicians made the introduction of new methods necessary. The formal lectures were cut down and emphasis was placed on instruction at the bedside,

clerical training, group teaching, seminars and conferences.

This tendency has continued after the introduction of the new study reform in 1959. At this period, Dr. John Lind was professor of pediatrics at the Pediatric Clinic of Karolinska Sjukhuset, having been appointed in 1956 when Wallgren retired. By this study reform, the course in pediatrics was again enlarged to 4 months with the same amount of weekly teaching, out-patient department instruction and clerical training. Until then the number of students had been limited to 25, but with the new reform 30 students were admitted. Another lecturer in pediatrics at each of the two pediatric clinics was appointed. During the course, the students received lectures and demonstrations in social (preventive) pediatrics by the lecturer of social medicine.

In 1960, an associate professor of child pathology, who takes part in the teaching of the students, was appointed at Karolinska Institutet. Since 1908, every student has had to assist in ward rounds and attend demonstrations and lectures at the Hospital for Infectious Diseases for 1 month. During the last 10 years, the care of newborn infants at the lying-in-hospitals has been the responsibility of pediatricians and has been included in the teaching of pediatrics.

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Effect of Posture and Insulin Hypoglycemia on Catecholamine Excretion in the Newborn[1]

by ROBERT E. GREENBERG[2], JOHN LIND and U. S. v. EULER

Release of catecholamines from their sites of production can result from a variety of stimuli. With the increasing recognition of differences between the physiological actions of noradrenaline and adrenaline, it is of interest that different forms of stimuli have been found to cause release of noradrenaline and adrenaline in varying proportions. Thus, adrenaline is selectively excreted in the urine in increased amounts following insulin (10), whereas carotid occlusion produces mainly noradrenaline release into the suprarenal venous blood of cats (15). When adults are placed in an upright position, an increased urinary excretion of both amines occurs, as reported by Euler, Luft & Sundin (11); this increase in release of predominantly noradrenaline is induced by the orthostatic fall of the blood pressure, acting over the baroreceptor homeostatic reflex mechanisms of the carotid sinus and aorta. The increase in noradrenaline excretion during erect posture appears, then, to provide a means of evaluating the degree of orthostatic stress imposed on the organism.

In view of the importance of catecholamine release in maintaining homeostasis in response to a variety of stressful stimuli, it was considered of interest to evaluate the response of newborns both to change in body posture and to insulin hypoglycemia, using urinary catecholamine excretion as evidence of increased or decreased production.

Methods

Urine was collected by strapping a 50 cc Erlenmeyer flask, curved at an angle of 90° at the top, to normal newborn males of varying ages. When evaluating the effect of change in posture on catecholamine excretion, a timed control collection was made after discarding the first observed voiding; as soon as the control urine was collected, the baby was strapped firmly to a board and placed in a vertical posture, which was maintained until the next timed collection was completed. When studying the effect of insulin, the babies were maintained in a recumbent posture throughout; insulin (Vitrum) was administered intramuscularly immediately after the control urine was collected. No attempt was made to fast babies, except from the start of the control collection period. Glucose water was administered orally at the conclusion of the post-insulin

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TABLE 1. *The effect of insulin on catecholamine excretion, (1 ng = 0.001 μg).*

							Pre-insulin					Post-insulin		
			Blood sugar (mg %)											
Age (days)	Weight (kg)	Insulin (units)	Fasting	30 min	60 min	90 min	Volume (cc)	Time (min)	Noradrenaline (ng/kg/min)	Adrenaline (ng/kg/min)	Volume (cc)	Time (min)	Noradrenaline (ng/kg/min)	Adrenaline (ng/kg/min)
2	3.77	1.2	77	67	36	29	3	175	.31	.048	34	330	.31	.61
3	4.53	1 5	88	66	64	51	9	270	.16	.078	18	130	.25	1.2
4	3.47	1.1	73	67	53	46	20	130	.32	.026	28	100	.50	.64
4	3.95	1.1	57	46	29	31	20	85	.28	.069	12	100	.13	.21
5	3.05	0.9	92	66	57	66	21	105	.39	.267	13	105	.078	.91
7	3.87	1.2	77	67	55	61	9	75	.21	.069	22	165	.20	.38
7	4.08	1.2	73	56	35	38	22	105	.14	.046	37	90	.15	.63
								Mean:	.26	.086			.23	.66
								S.D.:	± .089	±.081			±.14	±.33

P Noradrenaline = >.7; *P* Adrenaline = <.01.

collection. No untoward reactions to insulin were encountered in the doses used. All urine samples were acidified with 2–3 drops of 6 *N* HCl, frozen and analyzed usually within 24 hours.

Urinary catecholamines were determined according to the method of Euler & Lishajko (9). This method is based on the adsorption of catecholamines on an aluminum oxide column at pH 8.4 and elution with 0.25 *N* acetic acid. The eluate is neutralized to pH 6.3 with 2 *N* ammonia; the catecholamines are then oxidized with potassium ferricyanide and stabilized lutines are formed by the addition of alkali and ascorbic acid. The fluorescence is read with two filter sets in a Coleman photofluorometer, Model 12C, and the amounts of noradrenaline and adrenaline computed. The small quantity of catecholamines present in the urine samples necessitated using galvanometer deflections in the range of 3 to 15. The validity of the results obtained is supported by the following: (1) the close similarity of all blanks; (2) the regularity of changes between pre- and post-stimulus collections; and (3) the general agreement of control values with figures obtained on 24-hour urine collections from newborns using similar methods (when calculated as per minute excretion values) (12, 20). Values were calculated as nanograms (0.001 μg) excreted per kg body weight per minute.

Blood sugars were determined in duplicate by the method of Hagedorn & Jensen.

Results

Effect of insulin on catecholamine excretion

After the injection of 0.3 units per kg body weight of regular insulin intramuscularly, a reduction in the blood sugar of at least 20 mg % occurred in all infants studied, as shown in Table 1. Coincident with the fall in blood sugar, an increase in the urinary excretion of adrenaline occurred, as demonstrated graphically in Fig. 1. No change in noradrenaline excretion was found. The mean excretion of adrenaline in the pre- and post-insulin periods was 0.086 ± 0.081 and 0.66 ± 0.33 ng/kg body weight/minute, respectively. Similar values for noradrenaline were 0.26 ± 0.089 and 0.23 ± 0.14 ng/kg body weight/minute, respectively.

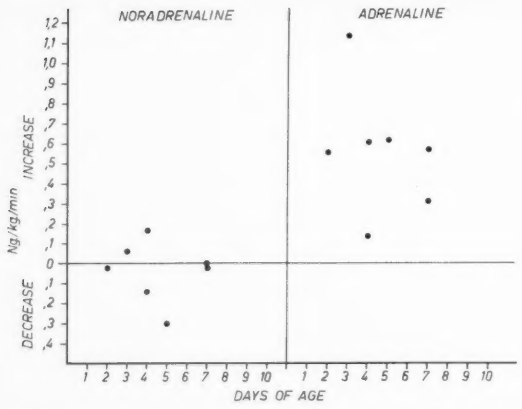

Fig. 1. The change in catecholamine excretion following insulin administration.

Effect of posture on catecholamine excretion

The urinary excretion of noradrenaline and adrenaline before and after newborns were placed in a vertical posture is tabulated in Table 2. The excretion of noradrenaline increased from a mean of 0.18 ± 0.081 to 0.45 ± 0.38 ng/kg body weight/minute with the assumption of a vertical position. Similar values for adrenaline were 0.035 ± 0.033 and 0.084 ± 0.066 ng/kg

TABLE 2. *The effect of change in position on catecholamine excretion.*

		Horizontal				Vertical			
Age (days)	Weight (kg)	Volume (cc)	Time (min)	Noradrenaline (ng/kg/min)	Adrenaline	Volume (cc)	Time (min)	Noradrenaline (ng/kg/min)	Adrenaline
1	3.72	14	330	.10	.019	6	70	.16	.089
1	3.36	20	690	.04	.004	7	210	.10	.007
1.5	4.20	2	75	.23	.045	2	78	.15	.000
2	3.46	6	240	.19	.018	6	120	.33	.027
2	3.07	6	300	.11	.005	3	130	.18	.036
2.5	1.96	9	310	.13	.021	4	325	.17	.075
2.5	3.24	15	945	.08	.017	6	270	.20	.086
2.5	3.86	11	180	.18	.089	10	80	1.4	.193
3	3.33	11	145	.27	.058	15	285	.62	.115
3	2.20	7	100	.18	.063	6	280	.31	.014
3	3.84	18	210	.33	.039	7	80	1.0	.150
3	3.92	15	180	.33	.010	4	160	.19	.012
4.5	2.75	7	105	.21	.000	15	245	.38	.159
5	4.20	8	330	.16	050	6	130	.29	.112
5	3.84	19	270	.12	.034	18	345	1.2	.193
5	3.67	24	150	.27	.120	3	80	.53	.053
6	3.24	7	140	.05	.000	18	65	.41	.029
6	3.86	35	210	.16	.038	7	105	.53	.119
			Mean =	.18	.035			.45	.044
			S.D. =	± .08	± .033			± .38	± .066

P Noradrenaline = < .01; P Adrenaline = < .02.

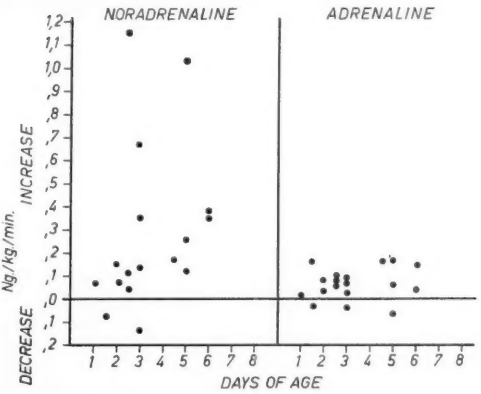

Fig. 2. The change in catecholamine excretion following vertical tilting.

body weight/minute, respectively. As depicted in Fig. 2, almost all of the infants studied demonstrated an increase in the excretion of both amines when placed in a vertical posture. The increase in noradrenaline excretion was greater, both in relative and absolute terms, than that of adrenaline.

Discussion

The presence of adrenaline, as well as noradrenaline, in the urine of newborns in amounts comparable to adults, in terms of micrograms excreted per unit weight, has been previously recorded (12, 20). It is now apparent that chromaffin tissue in the newborn is capable of elaborating increased amounts of adrenaline in response to a sudden reduction in the blood sugar level, comparable in degree to the response in adults (7). The increase in adrenaline secretion following the induction of hypoglycemia by insulin was initially demonstrated in 1924 by three separate groups (1, 3 14). Subsequent studies have both confirmed and extended these initial observations. A selective release of adrenaline was demonstrated both in the urinary excretion (1) and in plasma from the suprarenal gland after the administration of insulin (6). This effect could be abolished by denervation of the adrenals. Recently Vendsalu has shown an increased plasma level of adrenaline following insulin (17). Dunér noted that a decrease in the secretion of catecholamines from the adrenal ensued when the head alone was infused with glucose, suggesting the presence of a central nervous system receptor system (5). Since newborns are capable of responding to decreases in their blood sugar levels by increasing adrenaline production, the normally low blood sugar levels in the newborn period must coincide with a reduced threshold of such a central nervous system receptor mechanism.

The results of this study suggest that the newborn likewise responds to change in posture in a manner similar to the adult with respect to catecholamine excretion. Whereas the source of adrenaline

produced in response to insulin hypoglycemia is chromaffin tissue, whether intra- or extra-medullary in location, the source of noradrenaline released in response to postural changes is perhaps not as clearly defined. When the upright posture is assumed, an orthostatic fall in blood pressure, resulting from the pooling of blood in the splanchnic area and lower extremities, provokes reflex general stimulation of the vasomotor nerves by withdrawing sino-aortic baroreceptor inhibition from the vasomotor center, as reviewed by Hickler *et al.* (13). Since adrenalectomized patients excrete noradrenaline in similar amounts as normal subjects (7) and the excretion is greatly increased by tilting head upwards from recumbent position (8), it seems clear that adrenergic nerves are the source of noradrenaline excreted following postural changes. That the peripheral sympathetic nervous system largely determines the level of plasma noradrenaline values is supported by the studies of Weil-Malherbe & Bone (18), Munro & Robinson (16) and Vendsalu (17), in which it was found that the concentration of noradrenaline in venous plasma significantly exceeded that in arterial plasma with the reverse being true for adrenaline. In addition, Vendsalu has shown that venous plasma noradrenaline values were increased still further after tilting normal adults to a vertical position (17).

In adults, tilting produces a slight tachycardia and increase in diastolic blood pressure with no significant change in systolic pressure (2, 17). Young & Holland (19) found no change in blood pressure, obtained by palpation, in newborns under 5 days of age when studied during the first two minutes after tilting. After 5 days of age, a slight increase was observed; however, an increase in pulse rate was noted regardless of age. No hemodynamic observations were made in our studies. As is well known, changes in blood pressure do not adequately reflect adjustments that might be occurring within the circulatory system; marked vaso-constriction in some areas might well be balanced hemodynamically by vaso-dilatations in other vascular areas. Cross & Malcolm (4) have provided evidence that newborn rabbits, relatively immature at birth, possess functioning pressure and chemoreceptor reflexes. The findings in this report suggest that baroreceptor mechanisms are similarly functioning in newborn infants.

Summary

In newborn infants 1 to 7 days of age adrenaline excretion in urine was found to be greatly increased during insulin hypoglycemia and noradrenaline excretion markedly augmented upon change from horizontal to vertical posture as in adults. Accordingly, it may be assumed that both baroreceptors and the central nervous system receptor mechanism mediating the homeostatic response to hypoglycemia are functioning in the newborn period, the latter responding at a lower threshold.

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Treatment of the Undescended Testis

by C. G. BERGSTRAND and O. QVIST

The treatment of cryptorchism is in spite of all the literature on the subject still a matter of controversy. There is no general agreement regarding the time and character of treatment and with present knowledge it does not seem possible to definitely settle these questions.

The most important reason for treating cryptorchism is no doubt the fact that a testis left in a position outside the scrotum will ultimately undergo irreparable damage. In patients with bilateral involvement this means, possibly with a few exceptions, a total loss of fertility.

With regard to the many problems concerning management of the undescended testes it was thought of interest to study the immediate results of surgical and of hormonal treatment and compare the results with the findings in patients who had not received any treatment at all.

The question of how long a testis may remain in an abnormal position without permanent damage has been studied with the testicular biopsy technique but there is still disagreement of opinion. It is not the purpose of the present report to discuss this problem in full. It must, however, be mentioned that several authors (2, 5, 11, 12, 17) have found histological changes in the undescended testis at a relatively early age (5 to 10 years) but have also admitted that in some cases these changes may be due to constitutional defects. Other authors (1, 13, 15) have concluded that true degeneration does not occur before puberty. For these reasons it was thought justifiable in the present study to postpone treatment until near puberty especially as a previous investigation did not suggest that early treatment would give better result with regard to fertility (3).

The term *undescended testis* is defined in the present paper as a testis situated outside the scrotum and which by manipulation cannot be brought down into its proper place. The term *cryptorchism* is used as a synonym. With a *retractile testis* is meant a testis which occasionally is found in the scrotum or can be brought into a scrotal position by manipulation. An *ectopic testis* is usually defined as a testis that has deviated from its normal path of descent. Many surgeons consider a testis situated on the top of the external oblique aponeurosis as ectopic and find this position very common. Other authors state that this condition is relatively rare. As the problem has only a limited interest for the present investigation it will not be discussed and the term "ectopic testis" will not be used.

Materials and Methods

The patients for the study were selected in the following way. Among a total of 104 boys with cryptorchism seen at the surgical outpatient department at Kronprinsessan Lovisas Barnsjukhus from April 1954 to March 1956 37 patients were selected for immediate operation, 33 patients were referred to the endocrine outpatient department for hormone therapy and for 34 patients it was decided that no treatment should be given before early puberty. The selection of patients for these three groups was made at random. Bilateral cryptorchism was found in 21 patients and unilateral involvement in 83. Patients with retractile testes were as far as possible excluded from the study. Patients who, when first seen at the outpatient department, had a hernia and for this or other reasons had to be operated upon were also excluded.

It was decided that as a rule no treatment should be given before 10 years of age and not be postponed after 14 years.

The original scheme could, however, for different reasons not be strictly followed. Several patients did not come back for control examinations as arranged, other boys had to be operated upon as they developed a hernia or complained of inguinal pains and a small group of patients were treated in other hospitals. As a consequence a number of patients were found at the follow-up not to have been treated according to schedule. The hormone treated group and the group left without treatment were found to be considerably smaller than originally planned.

The technique for the orchiopexy will not be described in any detail. The inguinal canal was laid sufficiently open to permit a careful dissection and mobilization of the cord. The testis was placed in the scrotum and in certain cases fixed to the scrotal wall.

Chorionic gonadotrophin was given intramuscularly two times weekly in a dose of 600 I.U. for 6 or in some cases for 12 weeks. A few patients received a second course of injections.

The follow-up examination was made late in 1959, i.e. the time of observation for patients treated by orchiopexy or by gonadotrophin injections was at least 2 years. Of the original 104 patients 99 were personally re-examined, and 4 answered a questionnaire. One patient who at operation was lacking the right testis could not be found at the follow-up but was included in the study.

At re-examination the size, consistency and position of the testis was evaluated and the results of treatment were considered as good when these criteria were found to be normal. It might be emphasized that this does not necessarily mean future fertility. Sperm counts and testicular biopsies were not made at the follow-up. In a few cases biopsies were made in connection with orchiopexy.

Results

Group I. Patients selected for operation. The number of patients was 37 and of these cases 35 were operated upon. Three boys had bilateral cryptorchism. Two patients in this group had not been operated. They were found to be entirely normal at the re-examination and stated that spontaneous descent had occurred at the age of 11–12 and 14 years respectively. The results are shown in Tables 1 and 2 and may be summarized in the following way. In 26 patients, including 3 cases with bilateral involvement, the testicular position, size and consistency were entirely satisfactory. Testicular aplasia or atrophy was demonstrated at the operation in 5 cases. Only in a single case the follow-up examination showed a poor result: the testis could not be found. A questionable result was demonstrated in 3 patients: the testis was either situated high in the scrotum or found somewhat smaller than normal.

Group II. Patients selected for hormone

TABLE 1.

Number of patients	Age at operation	Primary result	Age at re-examination	Result of re-examination
2	7	questionable 1 poor 1	10–12	normal 2
2	9	[a] hypoplasia 2	12–13	testis not found 2
2	10	good 1 aplasia 1	14–15	normal 1 testis not found 1
5	11	good 4 poor 1	13–15	normal 4 questionable 1
9	12	good 7 poor 1 [a] hypoplasia 1	15–18	normal 7 poor 1 testis hypoplastic 1
8	13	good 5 questionable 2 aplasia 1	16–18	normal 6 questionable 1 testis not found 1
3	14	good 2 questionable 1	17–18	normal 2 questionable 1
1	15	good 1	18	normal 1

[a] Testis found hypoplastic at operation.

Immediate postoperative results and clinical findings at follow-up examination in 32 boys with unilateral cryptorchism treated by orchiopexy. *Good primary result:* Testis brought into correct anatomical position. *Questionable primary result:* Testis not brought down to the bottom of the scrotal sac. *Poor primary result:* Testis placed outside the scrotum. *Questionable result at the follow-up examination:* Testis situated high in the scrotum and/or somewhat smaller than normally. *Poor result at the follow-up examination:* Testis situated outside the scrotum and/or definitely atrophied.

treatment. The total number of patients was originally 33 and of these 24 had unilateral and 9 bilateral cryptorchism. Hormone treatment was given to 23 patients. Two patients were "by mistake" operated upon at 10 and 11 years of age respectively, without preoperative hormone therapy. In both cases a testicular atrophy was incidentally found at operation.

Eight patients did not receive any treatment at all. Most of them were considered too young when first seen and did not come back as arranged. At the follow-up examination 2 of these patients (1 with unilateral and 1 with bilateral cryptorchism) were found to be normal. Both had reached puberty and stated that spontaneous descent had occurred at an age of 11 and 13 years respectively. Two patients had developed a hernia and had to be referred for operation. In the remaining four patients the findings had not changed.

The results of the hormone treatment in the 23 patients are shown in Table 3. In 13 patients the hormone therapy was followed by operation. The results may be summarized in the following way. The hormone therapy was successful only in 5 patients (2 bilateral) out of 23. In 1 additional patient the testis was brought down into the scrotum but was definitely hypoplastic. The size of the testis had not increased at the time of re-examination. The result was questionable in one case. At

TABLE 2.

Number of patients	Age at operation	Primary result	Age at re-examination	Result of re-examination
1	right side 7 left side 8	good good	11	bilat. normal
1	right side 10 left side 11	good good	15	bilat. normal
1	bilat. 10	good	13	bilat. normal

Immediate postoperative results and clinical findings at follow-up examination in 3 boys with bilateral cryptorchism treated by orchiopexy. Definitions as in Table 1.

operation it was shown that one patient had hypoplastic testicles with suspected aplasia of the germinal cells and one patient had a one-sided testicular aplasia. The orchiopexy that followed the hormone treatment gave a satisfactory result in 4 cases and in 2 additional patients with bilateral involvement a satisfactory result on one side. The result was questionable in 3 cases, i.e. the testis was found somewhat smaller than normal or high in the scrotum. In two patients the result of the orchiopexy was very poor, i.e. the testis was found definitely atrophied at the re-exami-

TABLE 3.

Number of patients	Age at treatment	Result of hormone therapy	Number of pat. operated upon	Age at re-examination	Result of re-examination	
					Not operated	Operated
1	9	good 1	0	12	questionable 1	0
1	10	poor 1	1	13	0	questionable 1[a]
6	11	good 2 poor 4[a]	2	15–16	normal 2 poor 2	normal 2[a]
7	12	good 1 poor 6[b]	6	14–17	normal 1	normal 1 one side normal 1[a] questionable 1 poor 1 aplasia 1 "Klinefelter" 1[a]
4	13	good 1[a] poor 3[a]	1	18	normal 1[a] poor 2[a]	questionable 1
3	14	poor 3[a]	3	18–20	0	normal 1 one side normal 1[a] poor 1
1	15	good 1[a]	0	17	normal 1[a]	0

[a] one patient with bilateral cryptorchism.
[b] two patients with bilateral cryptorchism.

Immediate results of gonadotrophin administration and of orchiopexy following the hormone therapy. Clinical findings at follow-up examination of 23 boys. Definitions as in Table 1.

TABLE 4.

Number of patients	Age at descent	Age at re-examination	Result of re-examination	
3	11	11–14	normal	3
6	12[a]	12–17	normal	2
			one side normal	1[a]
			questionable	2
			atrophy	1
1	13	15	normal	1
1	14	15	atrophy	1
1	15[a]	16	normal	1[a]
3	>10[a]	14–15	normal	2[a]
			one side normal	1[a]
3	>11[a]	15–16	normal	3[a]
1	>12	17	atrophy	1
1	no descent	16	no descent	1

[a] one patient with bilateral cryptorchism.

Clinical findings at follow-up examination in 20 boys with spontaneous descent. Definitions as in Table 1.

nation. In spite of unsuccessful hormone therapy 3 patients had at the time of the follow-up examination not been operated.

Group III. Untreated patients. This group consisted originally of 34 patients and of these 25 had unilateral and 9 bilateral cryptorchism. For different reasons 13 patients (4 with bilateral cryptorchism) had at the time of the follow-up examination been operated upon. The result was entirely satisfactory except in one patient. This boy who had bilateral cryptorchism was operated at the age of 7 years. At the re-examination the right testis was considerably smaller than normal and situated outside the scrotum. One patient was given hormone therapy at the age of 13 years in another hospital. No effect was obtained. The remaining 20 patients (5 with bilateral cryptorchism) had at the time of the follow-up examination not received any treatment, and ranged in age between 11 and 17 years. Several of these patients who at the re-examination were found to be normal had failed to come for regular control examinations as arranged and were unable to definitely state when the descent had taken place. It was, however, obvious that in the majority the descensus had occurred after 12 years of age. The latest time of descent observed was 15 years. All patients had reached puberty, with exception of 2 boys with bilateral involvement. The findings at the follow-up examination are shown in Table 4.

The results may be summarized in the following way. Descent had at the time of the follow-up examination occurred in all of the 15 boys with unilateral cryptorchism except one. This boy was 16 years old and had reached puberty. In 2 pa-

tients, however, the testis was found somewhat smaller than normal and 3 patients showed a clearcut testicular atrophy. The result was satisfactory with regard to the position, size and consistency of the testis in 9 patients. Five boys had bilateral cryptorchism and of these 3 showed normal testicular findings whereas 2 boys only had an unilateral descent.

The result of treatment was also considered irrespective of in which group the patients originally were placed. It was found that of 63 patients operated upon, 42 (66 per cent) at re-examination showed normal testicular findings. The administration of gonadotrophin gave a good result in only 5 out of 25 patients and of 30 patients who had not received any treatment 16 showed normal conditions at the re-examination.

The number of patients who had reached an age of 13 years without treatment or had had spontaneous descent before that age was 48 and of these 14 showed at the follow-up examination an entirely satisfactory condition. Two additional patients with bilateral involvement showed descent on one side.

When the results were considered with regard to the original testicular position in Groups II and III it was found that in the 6 patients with descent after gonadotrophin administration the testes had been situated in the canal or outside the external ring when treatment was started. In the 19 boys with spontaneous descent (2 bilateral cases with one-sided descent) the testis had at the first examination been found in the canal in 2 cases, outside the external ring in 14 cases and in 3 cases the testis was not palpable.

Discussion

As previously mentioned it was decided that the patients of the three groups should be selected at random. If this was really achieved it could be expected that the incidence of different testicular positions should be the same in the groups. About 50 per cent of the patients in each group were found to have the undescended testis near the external inguinal ring at the initial examination. The testis was not palpable in 25 per cent and considered to be situated in the canal in 25 per cent. It must, however, be remarked that in the group that finally received hormone treatment the number of patients with the testis near the external ring were somewhat smaller than in the other two groups. The third group also underwent certain changes during the course of the investigation. Of the original 34 patients 13 were operated upon prior to the follow-up examination and in several of theses cases the testis was situated in the canal. Thus in the final group of untreated patients the testis in a majority of the cases was near the external ring. This must be kept in mind when the groups are compared.

It is obvious that the results found at the follow-up examination are different in the three groups. The best results were found in the patients treated by orchiopexy; 26 patients of 35 showed normal conditions and in 5 additional patients with testicular aplasia or primary atrophy it is not likely or possible that the result could have been improved by any form of treatment. This means that at most in 4 patients of this group the treatment can be regarded as unsuccessful. The figures seems to be in reasonable agreement with

the results of larger series e.g. Snyder & Chaffin, Gross & Jewett and Hallman *et al.* (7, 8, 16).

Compared with the results of orchiopexy the effect of hormone treatment appears very poor, only 5 of 23 patients showed a result that can be regarded as entirely satisfactory. In one patient later found to have a testicular aplasia on one side no treatment could have been of any benefit and it is likely that the same holds true for 4 additional patients where a pronounced testicular atrophy was found at the follow-up examination. It can not of course be wholly excluded that in these cases the gonadotrophin administration contributed to the testicular damage but this possibility seems rather unlikely in the light of recent investigations (4). The aplasia of the germinal cells found in one patient with bilateral cryptorchism and positive (female) "sex-chromatin" pattern is best regarded as a congenital defect. It is not likely that any type of treatment could have improved the condition. In one patient the result of the hormone therapy was not entirely satisfactory. The testis had moved out of the inguinal canal but not reached the scrotum. This boy was the youngest patient of this group. In summary it may be stated that at least in 11 patients out of 23 the hormone treatment must be regarded as a failure. In five of these cases a hernia was found at the subsequent operation.

In 13 patients the hormone therapy was followed by operation. If it is assumed that in 3 cases the operation could not reasonably have been of any benefit, and these cases are excluded, the results of the orchiopexy were entirely satisfactory in 4 patients, questionable in 3, poor in 1 and satisfactory only on one side in 1 case with bilateral cryptorchism. This group of patients treated both by hormones and by orchiopexy is too small for a comparison with the group where orchiopexy was the only treatment and it seems not possible to conclude that the results in the former group are less satisfactory.

The results of gonadotrophic hormone therapy reported in the literature have been very variable (for references vide Charny & Wolgin). The earlier reports claimed success in up to 100 per cent of the patients treated. There are still series published with very good results in a selected group of patients (4, 6) but generally the figures have in more recent investigations been lower. Judging from the literature it seems reasonable to expect descent from gonadotrophin administration in about 20 per cent of the patients. The result reported in the present paper (5 of 23 patients) corresponds rather well with this figure.

In the third group where no treatment was given the findings at the re-examination were entirely satisfactory in 12 of 20 patients (3 with bilateral cryptorchism). In 2 additional patients with bilateral involvement descent had occurred on one side. The exact number of "failures" is difficult to state also in this group as it is impossible when the testis was found smaller than normal or definitely atrophied to know whether this was due to a constitutional defect or could have been prevented by adequate treatment. It can therefore not be excluded that in the remaining 8 patients orchiopexy at an earlier stage could have given a better result.

The true incidence of spontaneous de-

scent during childhood is for different reasons very difficult to estimate and the figures given in the literature vary within wide ranges. Judging from larger series published 50 per cent seems to be an acceptable figure (9, 10, 14, 18). The number of patients with spontaneous descent and normal testicular findings (12 of 20 patients) reported here seems to be in agreement with these reports.

Many authors have come to the conclusion that gonadotrophin administration effect descent in only those patients whose testes ultimately would have descended spontaneously. With regard to the number of patients with spontaneous descent in the present investigation (12 of 20 patients) a more satisfactory result could perhaps have been expected in the hormone treated group (5 of 23 patients). As the number of patients in both groups is small the difference can hardly be regarded as significant and it may also be pointed out that in the hormone treated group the number of patients with the testis near the external ring was somewhat smaller than in the other groups.

As mentioned above the original group of untreated patients was reduced by operations performed prior to the follow-up examination. In the remaining patients the testis had in a larger number of cases a position near the external ring and it is possible that this fact contributed to the favourable result. About half of these patients showed normal testicular findings at the follow-up examination.

If 13 years is set as an age limit for "watchful waiting", which seems reasonable with regard to the increasing risk of testicular damage at the time of puberty, the figures for spontaneous descent are less favourable. About 45 per cent of the patients had reached this age without receiving any treatment and about one third of these boys were found to be entirely normal at the follow-up examination.

It is well known that in a certain number of patients with cryptorchism the undescended testis shows abnormalities which must be regarded as congenital. The frequency of this "primary testicular dysplasia" or "testicular dysgenesis" is not exactly known but seems according to several authors to be rather high. Charny & Wolgin give the figure 20 per cent of all undescended testes. It must be emphasized that for an evaluation of the true incidence of testicular dysgenesis a histological diagnosis is necessary and even then it may in some cases be difficult to exclude that the defects not are due to the undescended state of the testis. In the present investigation it could be established that at least in 19 cases one or both testes were atrophied or missing. As biopsies were not regularly made it is not possible to give the exact number of congenitally defective testes but it seems reasonably safe to state that in at least 10 of the 104 patients no treatment could have been of any value. In these cases testicular aplasia (3 patients) was demonstrated or the testis was found definitely hypoplastic at operation made at a relatively early age (before 11 years).

Summary

A follow-up study was made on 104 boys with cryptorchism not less than two years after treatment. The boys had been divided at random in three groups originally comparable with regard to testicular

position and to the age of the patients. In the first group treated by orchiopexy the findings were normal in 26 patients out of 35. In the second group treated with gonadotrophin the results were satisfactory only in 5 patients out of 23. The third group (20 patients) did not receive any treatment. Twelve boys were entirely normal and 2 boys with bilateral involvement had one normal testis in the scrotum.

It must be emphasized that a result, satisfactory from an anatomical point of view is no guarantee of future fertility It is therefore difficult to draw conclusions from the present investigation with regard to the choice of treatment. The high incidence of spontaneous descent found in this and in other investigations seems, however, to suggest a postponement of orchiopexy until near puberty as long as it has not been proved that the undescended testis undergoes permanent damage before puberty.

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Chronic Granulocytic Leukemia in Childhood

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In adults the chronic forms of leukemia constitute a large and significant group, the frequency of which predominates over that of the acute forms from the age of 25 years (cf. Wintrobe, 1956). From birth to 15 years the position is quite different. Acute leukemia is then relatively common, while the chronic type is unusual: the lymphatic form is extremely rare, and according to different statistics the granulocytic form constitutes only 5 % or less of all cases (Cooke, 1953; Opitz, 1954; Lightwood *et al.* 1960).

During the last 10 years the senior author has observed five cases of chronic granulocytic leukemia in children. Several of these were kept under careful observation over long periods. Among the special studies which were made, B_{12} analyses in the serum and the effect of Myleran therapy are worthy of mention.

Case Reports

Case 1. A boy, born March 17th, 1955, second child in a healthy family. From the age of 1 month the boy suffered almost constantly from infections of the upper respiratory tract. At the age of 4 months he was admitted to the department of pediatrics of the central hospital in Hudiksvall because of an "acute nephritis". The physical examination revealed small red papulous, partially encrusted eruptions on the scalp, the liver was palpable about 2 cm and the spleen about 3 cm below the arcus. Laboratory findings: Hb 10.3 g%, RBC 3.3 mill., WBC 32,200; differential count—st. 1, seg. 44, eos. 1, baso. 0, lympho. 46, mono. 8. After a few weeks the "nephritic" symptoms had disappeared and attention was now drawn to repeated boil-like infiltrations of various localisation, recurring and therapy-resistant infections of the upper respiratory tract, and to the changes in the white blood picture. The WBC count increased to 91,000 and a few promyelocytes, myelocytes and metamyelocytes appeared in the peripheral blood. The thrombocyte count was low with a mean value of about 50,000. Examination of the bone marrow revealed active leukopoiesis and slight hyperplasia of the reticuloendothelial system which was interpreted as a more or less normal reaction to the repeated infections. There were only very few megacaryocytes. After two months both the liver and spleen had increased considerably in size and the lymph glands had also become larger. One of them was excised for histological examination, but this did not reveal any specific changes. A large necrosis developed at the site of the excision. The development of the boy became more and more retarded and he failed to increase in weight, but in spite of the continuous infections, the anemia and the thrombocytopenia, the general condition remained surprisingly good.

At the age of 7 months the patient was transferred to the department of pediatrics of the University Hospital, Uppsala. On admission the liver was felt at the height of the umbilicus and the spleen reached the

crista iliaca. Moreover, a papulovesiculous eruption was noticed on scalp, face, back and legs. Blood examination revealed again anemia (Hb 10.9 g%), thrombocytopenia (60,000) and leucocytosis (56,800) with 3% promyelocytes, 5% myelocytes, 11.5% metamyelocytes and 8.5% pathological monocytes. Serum electrophoresis showed somewhat low albumin and high gamma-globulin values. ASTA was 5.0 units/ml. The B_{12} content of the serum was highly increased (4300 $\mu\mu$g/ml). In a new bone-marrow specimen the myelopoiesis was predominant with an accumulation of promyelocytes and myelocytes but quite a good representation of metamyelocytes and stab-forms. The diagnosis of chronic granulocytic leukemia seemed warranted and 10 X-ray treatments were administered. Thereafter the liver and spleen decreased in size, the WBC count was reduced to 15,000 with only very few immature cells remaining and the RBC and thrombocytes rose to almost normal values. But in spite of this improvement there developed new infiltrations of a bluish colour and with a tendency to spontaneous perforation and necrotisation, the pus containing *Staph. aureus* and *pyocyaneus* which needed treatment with erythromycin. The lymph glands increased continuously in size. At the end of the X-ray treatment the thrombocyte level had again fallen to 38,000. On December 13th, 1955, the boy was transferred back to the local pediatric department.

The subsequent course was characterised by failure to thrive, repeated infections of the respiratory tract, diarrhea and increasing spleno-hematomegaly in spite of treatment with Hydrocortone and Colcemid, the blood picture remaining quite constant with RBC between 3.2 and 3.6 million (sustained by iron medication), WBC between 13,000 and 43,000 (with up to 20% immature cells of all stages), and thrombocytes between 39,000 and 125,000. After therapy with Myleran (one month) the general condition improved somewhat, the liver and spleen decreased and the leucocyte count was further reduced. But after a short stay at home (about 1 month) skin infiltrations began again, together with several hematomas, and the WBC count rose again to 80,000. A new course of Myleran was begun but had to be discontinued after a short time because of thrombocytopenia (some values below 10,000), resulting in bleeding into the skin and from the mucous membranes. The boy recovered surprisingly well from an attack of chickenpox, but during the following months the general condition grew progressively worse with almost constant fever, leukemic infiltrations in the skin, enlargement of the spleen and liver, raised WBC count up to 532,000, anemia and thrombocytopenia. The boy died on January 29th, 1957, at the age of 1 year and 10 months, 1½ years after the onset of the disease. Autopsy was not performed.

Comment. This is a case with a very early onset, occurring already during the first half-year of life. It demonstrates the difficulties which may be sometimes encountered, at this age and at an early stage of the disease, in making a differential diagnosis, especially from infectious diseases. The true character of the disease was confirmed, however, by a strongly raised value of the B_{12} in the serum (4300 $\mu\mu$g/ml) and by a leucocytosis which in the final phase reached the very high value of 532,000 WBC per cmm.

An increased sensitivity to infection may occur in chronic granulocytic leukemia in adults but is usually not a prominent feature. In this child both upper respiratory and cutaneous staphylococcal infections were found. These can undoubtedly have contributed to leukocytosis, enlargement of spleen and liver, and even to the general lymphadenophathy. Of the other striking features the periodic lymphocytosis (max. 16,000; cf. also Case 3) may be mentioned, and the absence of thrombocytosis—in certain periods there was a

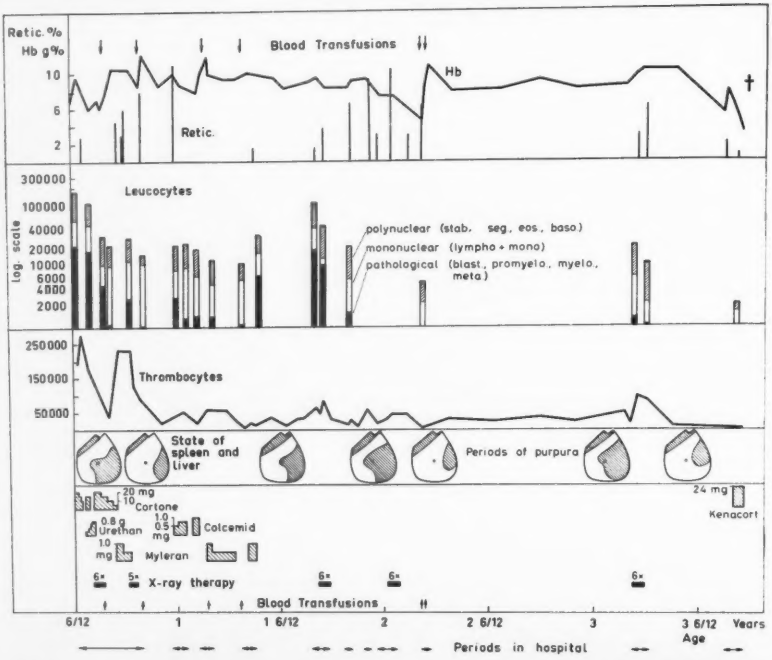
TABLE 1. *Some hematological findings in case 1.*

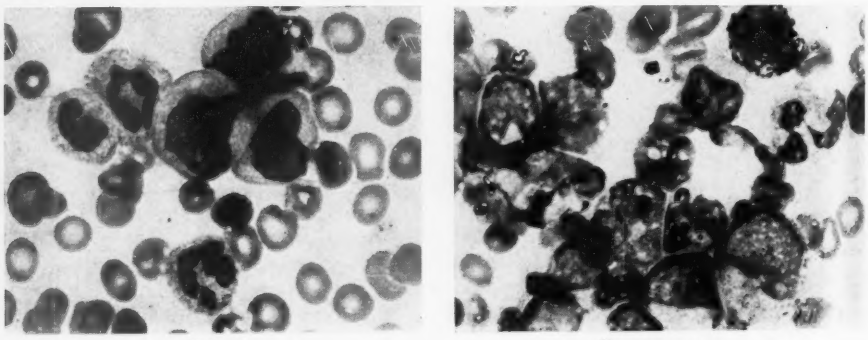
Age, years	Hb g%	Platelets	WBC	Blast.	Promyelo.	Myelo.	Meta.	St.	Seg.	Eos.	Baso.	Lympho.	Mono.	Path. mono.
4/12	10.3		32.200	—	—	—	—	1	44	1	—	46	8	—
5/12	10.6	54,000	31,200	—	1	2	4	6	26	3	1	51	6	—
5/12	9.5	64,000	31,000	—	—	—	—	6	34	2	—	56	2	—
7/12	10.9	60,000	56,800	—	3	5	11.5	6.5	21	1.5	—	30	13	8.5
8/12	11.5	43,000	15,200	1	—	2	3	4.5	40	—	—	11.5	20	19
9/12	11.8	38,000	13,300	—	—	2	2.5	2	42.5	—	0.5	12	31.5	7
11/12	10.1	123,000	43,000	—	—	3	3	7	47	1	—	24	10	5
1 2/12	9.3	28,000	78,800	2	2	3	3	7	28	3	4	41	3	4
1 7/12	8.9	10,000	532,000											

pronounced thrombocytopenia. This was noted before the commencement of any specific treatment, but it became intense during the second period of Myleran therapy.

Case 2. A boy, born on November 25th, 1954, fourth child. One brother died one day after delivery (probably cerebral hemorrhage); the mother had anemia and albuminuria during the last two months of this pregnancy. The boy has always had a large abdomen ("like a frog") but was otherwise quite healthy up to the age of 5 months when the abdomen began to extend more and more, contrasting strikingly to the thin chest and extremities. In spite of a good appetite he failed to thrive, and became pale. On admission to the hospital on May 31st, 1955, at the age of 6 months, he appeared pale and thin with a strikingly large abdomen, over which the veins were dilated. The liver was palpable about 4 cm below the arcus, the spleen enormously enlarged, disappearing behind the symphysis at its lower edge and reaching a line 5 cm to the right of the umbilicus. Laboratory findings: Hb 7.8 g%, RBC 2.6 mill., reticulocytes 10.6 %, WBC 171,200; differential count—blast cells 8, promyelo. 7.5, meta. 5.5 st. 4.5, seg. 18.5, eos. 11, baso. 5, lympho. 18.5 mono. 15.5. Nucleated red cells, 5 per 100 WBC. Thrombocytes 196,000. Serum iron 59 gamma%. Non-protein N 44 mg%. B_{12}-concentration in the serum 4000 $\mu\mu$g/ml. The bone marrow showed a predominance of the myelopoiesis with mostly myelocytes and metamyelocytes, and only very few myeloblasts. The erythropoiesis did not show any abnormalities, the number of reticuloendothelial cells was slightly increased.

The diagnosis of chronic granulocytic leukemia seemed definite and therapy with Cortone, later combined with Urethan was tried, but this did not exhibit any effect on the enlarged spleen or the leucocytosis. A series of six X-ray treatments was therefore given, which resulted in a rapid decrease in the number of white cells with disappearance of all pathological elements, and in a decrease in the size of the spleen. A transitory fall in the thrombocyte count to 40,000 was also noticed, however, resulting in petechiae. The B_{12}-concentration in the serum had decreased to 600 $\mu\mu$g/ml after X-ray treatment. Because of a recurring tendency to increasing WBC and further enlargement of the spleen in spite of treatment with Myleran, a new series of X-ray treatments was given in Sept. 1955 with the same beneficial effect as before, but again resulting in a thrombocytopenia, whereas the hemoglobin concentration was maintained at a satisfactory level by means of a few blood transfusions. On discharge from hospital on Oct. 1st, 1955, at the age of 10 months, the general condition





Blood Bone marrow

Fig. 1 (Case 2). Chronic granulocytic leukemia. Male, age at time of diagnosis 6 months.

of the patient was fairly good. As may be seen from Fig. 1, the leucocyte count began to rise again a few months later; the thrombocytes remained persistently at a very low level—resulting in periodic petechial eruptions—and the spleen gradually increased in size in spite of treatment with Colcemid and Myleran. At the age of 1 year and 8 months a further series of X-ray treatments had to be given, once more with quite good effect on leucocytosis and general condition but without any measurable decrease in the size of the spleen. During the following 1½ years the boy was in a fairly

good state apart from frequent infections of the upper respiratory tract, several purpuric rashes and occasional gastrointestinal symptoms. His mental and physical development during this period were normal. A further series of X-ray treatments at the age of 3 years and 2 months had a moderately good effect, but four months later the general condition became worse. Profuse bleeding from the nose and in the skin resulted in a marked fall of the hemoglobin level in spite of blood transfusions and Kenacort medications. One month after the onset of these symptoms the patient died, showing physical signs of bilateral bronchopneumonia. Death occurred at the age of 3 years and 8 months, 3 years and 2 months after the diagnosis had been made. The autopsy revealed multiple pulmonary hemorrhages as the immediate cause of death and a marked infiltration of the bone marrow, spleen and lymphglands with myeloid elements, partly of atypical appearance and with a strikingly high number of eosinophils.

Comment. The complete picture of chronic granulocytic leukemia was present already at the age of 6 months. There is reason to believe that the disease had existed for a considerable time before this. The first B_{12} analysis showed a characteristically raised value (4000 $\mu\mu$g/ml). The course is seen in Fig. 1—it extended over a period as long as $3\frac{1}{4}$ years. A pronounced sensitivity to infections of the upper respiratory tract was noted also in this case. X-ray therapy showed striking results on repeated occasions, while various other therapeutic attempts, including Myleran, exhibited poor or no effect. In this case, as in several of the others, it was difficult to avoid thrombocytopenia and tendency to bleeding during treatment.

Case 3. A girl, born May 22nd, 1949, fourth child in a healthy family. In good health up to the age of 5 months, when she had a bilateral otitis media with an unusually protracted course. She was admitted to the department of pediatrics of the central hospital in Visby on December 3rd, 1949, because of persistent otorrhoea. Physical examination revealed no abnormalities other than the chronic otitis. Laboratory findings: Hb 7.7 g%, WBC 35,600; differential count—myelo. 8, meta. 10, st. 13, seg. 30, eos, 3, baso. 0, lympho. 35, mono. 1. The anemia responded well to iron therapy and the general condition improved. However, three weeks later the liver and spleen became palpable. The bone marrow showed a maturation arrest both in myelopoiesis and erythropoiesis, a slight eosinophilia and a hyperplasia of the RES. Five weeks later the leucocyte count had risen to 58,000. Differential count: myelo. 6, meta. 2, st. 7, seg. 20, eos. 2, lympho. 51, mono. 12. During the following months the liver and spleen increased progressively in size. The child was therefore treated with several blood transfusions, X-rays and Urethan, after which the leucocyte count decreased to 9600 with still a few immature cells in the differential count, and the liver and spleen were reduced in size. On March 28th, 1950, the child was transferred to the department of pediatrics of the Norrtull hospital in Stockholm. On admission the girl was in a satisfactory general condition. Eczematous eruptions were seen on the head, shoulders and genito-anal region. Liver and spleen were enlarged, the edge of the latter being palpable about 5 cm below the arcus, and a slight swelling of the lymph nodes was noted. Laboratory findings: Hb 8.1 g%, thrombocytes 57,000, WBC 19,400; differential count—a few myelo., st. 7, seg. 48, eos. 5, baso. 0, mono. 5, lympho. 35. Serum bilirubin 0.6 mg%. Non-protein N 33 mg%. Bleeding time 2 min, coagulation time 1 min. Histological examination of an excised lymph node showed a hypertrophy of the reticulo-endothelial cells and an infiltration with eosinophils. The girl was again treated with Urethan during the next three weeks with a moderate effect upon the WBC count

TABLE 2. *Some hematological findings in case 3.*

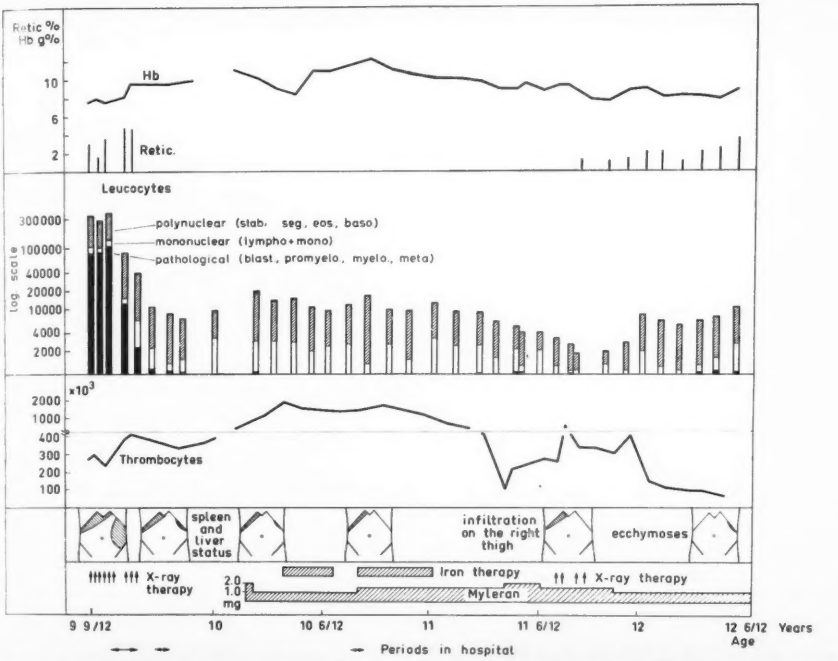
Age, years	Hb g %	Platelets	WBC	Blast.	Promyelo.	Myelo.	Meta.	St.	Seg.	Eos.	Baso.	Lympho.	Mono.
$\frac{6}{12}$	7.7		35,600	—	—	8	10	13	30	3	—	35	1
$\frac{8}{12}$	9.6	128,000	58,000	—	—	6	2	7	20	2	—	51	12
$\frac{9}{12}$	9.5	89,000	9,600	1	—	4	2	6	45	3	—	31	5
$\frac{10}{12}$	8.1	57,000	19,400	—	—	a few	—	7	48	5	—	35	5
$1\frac{2}{12}$	11.8	80,000	44,200	—	—	—	—	9	23	8	—	55	5
$1\frac{8}{12}$	9.6	83,000	43,700	—	—	15	4	8	28	1	—	34	10

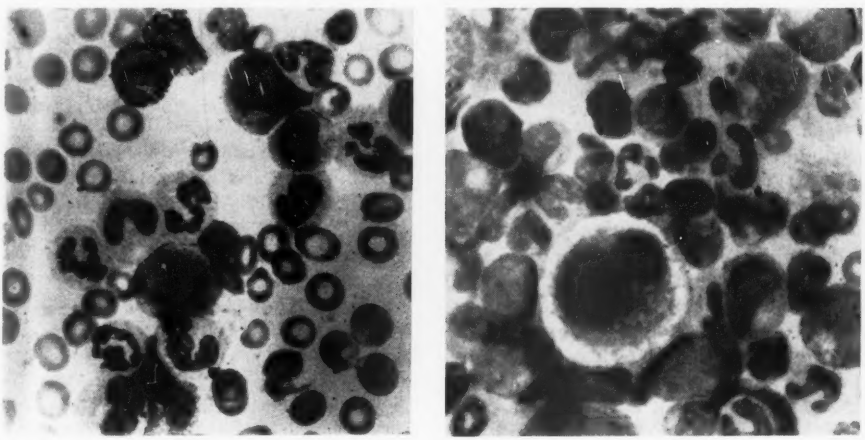
and splenic enlargement. She was discharged from the hospital in good condition on April 20th, 1950.

After 2 months of fairly good health the child had another protracted otitis media, which did not respond to antibiotics, and the general condition deteriorated gradually. On admission to the Norrtull hospital on July 10th, 1950, at the age of 14 months, the lymph glands, liver and spleen were enlarged, the latter extending to below the umbilicus. Hb was 11.8 g%, thrombocytes 80,000, WBC 44,200 with absence of all immature cells. Penicillin was given and a new course of Urethan begun, again resulting in a decrease of the WBC count, but without any effect upon the size of the parenchymatous organs. She was discharged from the hospital on July 10th, 1950, in improved state. During the following months the child appeared quite healthy, but in November 1950 she had to be treated again with Urethan for 8 days because of increasing WBC count. In spite of hematological improvement the child had repeated infections of the respiratory tract. In December 1950 she developed migrating pneumonia, and died on February 2nd, 1951, 1 year and 2 months after the first hospitalisation. Autopsy was not performed.

Comment. As in cases 1 and 2, this is a child with a very early onset of the disease, i.e. before the age of 6 months. In this case also there was a markedly increased tendency to infection (recurrent otitis, upper respiratory infections and pneumonia). This is the only girl in the material, and the diagnosis lacks the evidence of a B_{12} analysis and a leucocytosis over 100,000. The clinical data taken together, the reaction to X-ray therapy and Urethan, and the fatal outcome after a course of $1\frac{3}{12}$ years, support the diagnosis of chronic granulocytic leukemia, but at the same time point to the difficulties which may occur in making a definite diagnosis at an early age.

Case 4. A boy, born March 16th, 1948, fourth child in a family with high incidence of tuberculosis. Always in good health to the age of 8 years when he consulted a physician because of a hematoma on the foot. The physician noticed an anemia which was improved by iron therapy. At the age of 9 years and 9 months his appetite became poor and the boy was restless during the night. He had no pains and no other pathological signs. On admission to hospital on Dec. 12th, 1957, the boy appeared pale; the liver was palpable about 2 cm below the arcus and the spleen was enormous, reaching the crista iliaca at its lowest point. Laboratory findings: Hb 7.6 g%, RBC 2.6 mill., reticulocytes 3.0%, platelets 268,000. The sedimentation rate was accelerated (35 mm). There were 336,000 white cells: blast. cells 3, promyelo. (eos. and baso.) 3, myelo. (eos. and baso.) 4, metamyelo. 15, st. 2[illegible].5, seg. 37.5, eos. 4.5, baso. 6, lympho. 6, mono. 9.5. Nucleated red cells 4 per 200 white cells. The bone-marrow punctate showed a picture





Blood Bone marrow

Fig. 2 (Case 4). Chronic granulocytic leukemia. Male, age at time of diagnosis $9\frac{9}{12}$ years.

consistent with chronic granulocytic leukemia. The total serum protein was 6.8 g%, serum electrophoresis showed somewhat low albumin and increased alfa$_2$-globulin concentration. The B_{12}-concentration in the serum was 7300 $\mu\mu$g/ml. The patient was given nine X-ray irradiations to the spleen, which resulted in a significant improvement

of all symptoms. The spleen was reduced to an almost normal size, the hemoglobin rose to 9.6 g%, the leucocytosis decreased to a value of 41,700 with absence of blast-cells. During the following months the white cells continued to decrease without treatment and the boy was in excellent condition. He was checked regularly at the out-patient department of the clinic.

The further course is evident from Fig. 2. A striking feature in the repeated blood examination was the extremely high number of thrombocytes (highest value 1,952,000 on July 4th, 1958, 7 months after X-ray treatment). In spite of the absence of clinical symptoms, treatment with Myleran was begun in June 1958. During a short period in the spring of 1958 the boy had quite abundant nose-bleedings, which were cured by local cauterization. The nose-bleeding resulted in an anemia (Hb 8.4 g%) which was treated successfully by iron therapy. At the age of 11½ years (in Nov. 1959) the patient had an acute infection of the upper respiratory tract, followed by pains due to an infiltration on the left thigh. He was then again admitted to hospital for X-ray treatment of the infiltration. On admission a striking hyperpigmentation on the abdomen and the genico-anal region was noticed. During the following months the general condition was somewhat worse, the white cells were at a very low level and the anemia was more pronounced than usual.

After a period of fairly good health the situation has again deteriorated in the summer months of 1960. Following a painful swelling of the right elbow region the boy was hospitalized again on Sept. 12th, 1960. On admission the following values were obtained: RBC 3.1 mill., WBC 9600 (blast-cells 6.5, promyelo. 1, myelo. 2, meta. 7.5, st. 23, seg. 47, eos. 3, baseo. 3, lympho. 4.5, mono. 2.5), nucleated red cells 6 per 100 WBC, thrombocytes 70,000. Bone-marrow aspiration gave dry tap in the sternum but was successful in the iliac crest. The number of nucleated cells in the marrow was very low without signs of myeloblastic proliferation. These features together with the occurrence of a considerable number of normoblasts in the blood and X-ray signs of sclerotic changes in the bones may be indicative of supervening myelofibrosis.

Comment. This boy was about 10 years old when the disease was established. For two years previously a tendency to react to traumata with hematomas had been observed. At the first investigation the thrombocyte level was normal. It later rose over a long period to values much above normal, such as have been observed in many adult cases. The B_{12} value at the time of the first examination was 7300 $\mu\mu$g/ml. X-ray therapy of the spleen showed excellent results on repeated occasions. Similarly, X-ray therapy suppressed a local reaction and pain in one leg, rapidly and for a long period. Myleran has been given for a period of 28 months, and in doses of 1.0–1.5 (2.0) mg, and has exhibited good effects as maintenance therapy. This patient, the only one still alive, has during the last few months developed signs, which may be indicative of myelofibrosis.

Case 5. A boy, born June 4th, 1944, third child in a healthy family. As an infant operated on for intussusception but otherwise always in good health. At the age of 7 years he had some periods with moderate fever without any plausible cause, sometimes accompanied by transitory arthralgia. The physician observed only a slight enlargement of the lymph glands of the neck, in the axillae, and the cubitae. Liver and spleen were just palpable. There were 54% lymphocytes (a few of which atypical), and 6.5% plasma cells in the blood picture. Paul Bunnel test neg. One year later recurrence of slight fever of unexplained origin and in the blood a number of atypical cells such as occur in "pseudomononucleosis"; moreover an eosinophilia of 15%.

In the autumn of 1955 (at the age of $11\frac{1}{2}$ years) the boy felt tired, decreased in weight and complained of abdominal pains. On one occasion he also had a profuse nose-bleeding. In the beginning of November he noticed small painless infiltrations in the skin of the extremities and large hematomas began to appear after insignificant traumata. He was admitted to the department of pediatrics at the University Hospital, Uppsala, on Nov. 17th, 1955. The physical examination revealed a generalized swelling of the lymph nodes, and an enlargement of the spleen which reached the umbilicus at its lower edge and was firm and painless. Examination of the blood showed an anemia (Hb 8.6 g%) and a WBC count of 251,000. Differential count: blast-cells 1, promyelo. 1.5, myelo. 15, meta. 19.5, st. 20.5, seg. 26, eos. 5, baso. 3, lympho. 6, mono. 2.5. Moreover 2 nucleated red cells per 200 white cells. Thrombocytes 63,000. Sedimentation rate 37 mm. B_{12}-concentration in the serum 9500 $\mu\mu$g/ml.

During November and December 1955 the patient was treated with X-rays which resulted in a leucopenia (WBC 2180) and thrombocytopenia (25,000), while the hemoglobin concentration increased to values above 10 g%. The spleen decreased rapidly in size and was no longer palpable at the end of January 1956, by which time the general condition had become excellent. The B_{12}-concentration in the serum had fallen to 460 $\mu\mu$g/ml. During the following months the number of white cells increased gradually, more immature elements appeared in the peripheral blood, and the boy complained of abdominal pains. But in spite of this relapse the hemoglobin values continued to rise up to 14 g% and the thrombocytes up to 140,000. On April 4th a course of Colcemid was begun, but in spite of high dosage (up to 8 mg pro die) the WBC count continued to increase (above 100,000 in the beginning of June 1956), and the spleen was palpable again. A new series of X-ray treatments was therefore administered. After this series the boy was given Myleran for about 1 month, and finally a normalisation of the blood picture was obtained. A further relapse in September 1956 responded but not sufficiently well to prolonged therapy with Myleran. Two further X-ray tratments in April and June 1957 resulted in a fall of the WBC count to values between 10,000 and 20,000, but with as much as 20% blast-cells. Purinethol was therefore given for 1 month. Because of a rapid rise in the WBC count in spite of this medication, the therapy was changed, and Myleran prescribed again. Already before this period the boy had complained of pain in the left knee and thigh and roentgenological examination revealed a periostal reaction. After a short remission rapid deterioration again ensued with intense pains in the extremities, only temporarily allayed by X-ray irradiation. The general condition grew gradually worse in the autumn of 1957. As a result of therapy with Myleran and Purinethol, the white cell values fell to below 1000, and there were more than 50% blast-cells. Other signs of bone-marrow aplasia appeared in the form of progressing anemia and thrombocytopenia in spite of repeated blood transfusions. The intense pains required high doses of morphine derivatives. The boy died on November 24th, 1957, $2\frac{1}{12}$ years after the diagnosis of chronic granulocytic leukemia had been made. Autopsy was not performed.

Comment. In this case, which was diagnosed at the age of $11\frac{1}{2}$ years, the disease picture bears more resemblance to that of the adult. The onset was insidious, with vague prodromal symptoms. On two occasions, $4\frac{1}{2}$ and $3\frac{1}{2}$ years respectively before the diagnosis was made, blood tests had been performed for suspected virus infections, possibly mononucleosis. On the first occasion a slight lymphadenosis and a just palpable spleen had been noted. The differential count on the first occasion showed a plasma cell increase (6.5%), and on the second occasion a marked eosinophilia (15%) and in both cases a number of "atypical lymphocytes".

TABLE 3. *Some hematological findings in case 5.*

Age, years	Hb g %	Platelets	WBC	Blast.	Promyelo.	Myelo.	Meta.	St.	Seg.	Eos.	Baso.	Lympho.	Mono.	Plasma
11 5/12	8.6	63,000	251,000	1	1.5	15	19.5	20.5	26	5	3	6	2.5	
11 6/12	10.3	346,000	21,100	—	—	6.5	8.5	13	51.5	1	4.5	3	7	—
11 7/12	10.5	25,000	2,180	—	—	—	0.5	2.5	61.5	3.5	1	13.5	17.5	—
11 9/12	14.0	137,000	18,800	—	—	4	3.5	7.5	61.5	0.5	3.0	10.5	9.5	—
12	11.8	133,000	105,700	0.5	2.5	11	17	25.5	36	1	1.5	2.5	2.5	—
12 1/12	11.5	160,000	3,200	—	—	—	—	2.5	69	4.5	2	11	11	—
13 1/12	8.0	119,000	17,700	18.5	13	21.5	17	14	14	—	—	2	—	—
13 3/12	10.3	317,000	106,500	5.5	3.5	17.5	20	13	14	—	—	10	16.5	—
13 5/12	6.6	10,000	300											
13 6/12	7.0	43,000	17,200	53	13.5	12.5	3	2	4.5	—	0.5	9.5	1.5	—

The appearance of large hematomas after trauma revealed the disease. X-ray therapy to the spleen produced in this case also a very effective, and at first a long-lasting result. The B_{12} value in the serum was initially very high (9500 $\mu\mu$g/ml) but fell to a value within normal limits (400 $\mu\mu$g/ml) during successful therapy. Similar changes in the remission period have been described previously for adults (Mollin & Ross, 1955). During the further course of the disease Myleran was administered in doses of 1–2 (6) mg and for a total period of 13 months. The effect was favourable, but could not be compared with X-ray therapy as regards the influence on the spleen and blood picture. Colcemid did not show any definite effect, and the result of Purinethol treatment in the terminal blast stage was uncertain.

Discussion

The largest material of chronic granulocytic leukemia in children so far presented is that by Cooke (1953), comprising 15 cases in all. This material was collected before Myleran therapy was introduced in the clinic. Otherwise some smaller series of cases (Gasser, 1946; Gilly & Germain, 1958; Vignetti & Felici, 1959) and a considerable number of single observations (eg. Andersen & Kringelbach, 1951; Fox & Hunter, 1954) have been published.

The cases presented in this paper, although limited in number, illustrate well some of the special features related to childhood age and in addition give the results of B_{12} analysis of the serum and notes on the effect of Myleran therapy. Only exceptionally have these aspects been commented upon in earlier observations dealing with chronic granulocytic leukemia of childhood.

Frequency

The population immediately served by the pediatric department in Uppsala is roughly 200,000. In addition cases are transferred from pediatric departments in other parts of the country, especially from the northern regions. The distribution of leukemia cases with regard to the type of the disease and the place of residence of

TABLE 4. *Leukemia in the age group 0–15 years. Department of Pediatrics, Uppsala, 1950–59.*

Type	Uppsala area	Other areas	Total
Acute	9	12	21
Chronic granulocytic	3	1	4[a]
Chronic lymphocytic	0	0	0

[a] Case 3, which was observed by the senior author when he was still attached to the Nortull Hospital, Stockholm, is not included in this table.

the child for the 10-year period 1950–59 may be seen in the following table.

The proportion for chronic granulocytic leukemia in this material is considerably higher than the figure of ca. 5 % mentioned above. In view of the small number of cases, however, this may be simply due to random variations.

Clinical Picture

Onset. The signs which caused the first visit to a doctor were varying: recurrent infections (Nos. 1 and 3), large abdomen (No. 2), and tendency to hematomas (Nos. 4 and 5). It is reasonable to assume that the disease existed a considerable time before medical advice was first sought. Four out of five children showed pronounced clinical signs and laboratory findings already at the first medical examination.

One of the children (No. 5) had been examined several times for other reasons before the leukemia picture became evident. Blood investigations, also including differential counts, had been carried out, $4\frac{2}{12}$, 3 and $2\frac{2}{12}$ years before the establishment of the disease. The results were as shown in Table 5.

Symptomatology. The basic features are the same as in adults, i.e. tiredness, loss of weight, abdominal discomfort from the often considerable splenic enlargement, hemorrhagic manifestations and later on rheumatic pains and fever of unexplained origin.

Certain particular observations in this material are worthy of mention. In the small children (Nos. 1 and 3 especially), there was an increased susceptibility to acute infections. There also seemed to be in these very young children a more

TABLE 5. *Hematological data, obtained before manifestation of disease in case 5.*

Age, years	Hb g %	WBC	Pathological cells	St.	Seg.	Eos.	Baso.	Lympho.	Mono.	Plasma
$7\frac{3}{12}$	13.0	6,500	—	1.5	44	2	1.5	44[a]	6.5	6.5
$8\frac{5}{12}$	12.4	7,400	—	5	40	12	2	36[a]	5[a]	—
$9\frac{3}{12}$		4,500				15				
$11\frac{5}{12}$	8.6	251,000	37	20.5	26	5	3	6	2.5	—

[a] few "atypial".

pronounced tendency to thrombocytopenia and purpura, even during periods of adequate treatment.

Lymphadenopathy is rarely seen in adult cases, except perhaps for the terminal phase. In several of our patients (Nos. 1 and 3, with very early onset, and No. 5) a generalized swelling of the lymph glands was observed, and in the young children there was also at times an increase of the absolute numbers of lymphocytes. This might to some extent be an "age specific" mode of reaction. One of the children (No. 4) has shown a gradually increasing, dull brownish-grey pigmentation. It is possible that this is connected with the Myleran therapy, in association with which similar pigmentation has been described previously (Wilkinson & Turner, 1959). During the course of the disease the two older children (Nos. 4 and 5) exhibited very painful local reactions in the extremities with swelling and tenderness, only to a certain degree reflecting definite changes in the bony structures visible on X-ray. These symptoms were alleviated by X-ray therapy.

Laboratory findings. The blood and bone-marrow pictures were essentially those well known in adults. The values for basophiles, usually raised to 2–5 % in adults were found increased more regularly in cases 4 and 5, sporadically in cases 1 and 2. Eosinophilia, in itself more difficult to evaluate with respect to origin was found continuously or periodically in all cases. The thrombocyte values were low before the commencement of therapy in at least two of the cases (Nos. 1 and 5), and the tendency to thrombocytopenia during treatment was seemingly more pronounced than in adults.

B_{12} analysis in the serum was carried out in 4 of the children. As has been similarly observed in adults (Mollin & Ross, 1955) the values were greatly raised, i.e. between 4000 and 9500 $\mu\mu$g/ml, compared with normal variations in children and adolescents of between ca. 300 and 1300 $\mu\mu$g/ml (Killander, 1957). In adults abnormally high B_{12} values have been observed in cases of acute leukemia but in the pediatric age group this was not found in a group of 14 cases (Killander, 1956). And in other diseases, e.g. infections, such high B_{12} values as are here under discussion, have not been observed. After successful therapy a decrease to values within normal variations was noted in the two cases (Nos. 2 and 5) in which a second analysis was performed.

Course. The duration from the first visit to a doctor until death varied in the three patients with a very early onset (Nos. 1, 2 and 3) between $1\frac{3}{12}$ and $3\frac{3}{12}$ years, and for patient No. 5 with a late onset it was $2\frac{1}{2}$ years. Patient No. 4 is still alive after $2\frac{9}{12}$ years. In comparison it may be mentioned that in a material from all age groups, collected by Tivey (1954) and comprising 1090 patients, the mean survival period from "onset" to death was 2.70 years. The frequency of cases with a course of 5 years or longer in this material was 22 %. In Case 4, still alive, the development during the last few months may be indicative of myelofibrosis. Such a profound disturbance of bone-marrow function has been observed as a late event in adult cases, before as well as after the introduction of Myleran therapy (cf. Dameshek & Gunz, 1958) and may be more common than is generally realized.

Therapy

The methods of treatment most used for adults today (cf. Wilkinson & Turner, 1959) are Myleran and X-ray therapy. In resistant cases TEM and P^{32} may be worth trying, and in the final phase purine or folic acid antagonists.

Only a few cases of chronic granulocytic leukemia in childhood treated by Myleran have been reported, since this method of treatment was first introduced in 1953. In our cases Myleran was administered for shorter or longer periods in four of the five cases. In the two older children the effect was striking, and at least in Case 4 fully comparable with that usually seen in adults. It cannot be excluded, though, that the myelofibrosis now probably present may have something to do with the treatment which in this case has included continuous Myleran medication over very long time (cf. Fig. 2). In the two small children the drug was tested for too short a time to permit a final evaluation, but the impression was that the desired selective effect on the granulocytopoiesis and the adverse tendency to pancytopenia were difficult to balance. X-ray therapy, on the other hand, gave good results, even if complete control of the hepato-splenomegaly could not be obtained in the small children without administering doses which exposed the child to the risk of a too intensive effect on the bone marrow.

It is of interest to note how many of the children had remissions of such a kind that they could be regarded, according to adult standards, as completely satisfactory. A remission in chronic granulocytic leukemia seldom means a complete normalization of the blood and bone-marrow pictures, such as is nowadays frequently observed in acute childhood leukemia. Experience from adult medicine shows that the general condition of the patient with chronic granulocytic leukemia is often better and the risk of "excess" reactions of an aplastic type less, if a leucocyte value of 20–30,000 or even more in the peripheral blood is accepted, providing the cells are composed essentially of mature elements, the hemoglobin and thrombocyte values are not below the lower normal limit, and the spleen does not show more than at most slight enlargement. If the therapy results in our five cases are regarded on this basis, the conclusion is as follows.

All cases reacted favourably to the therapy at first. The effect of X-rays on the spleen is as a rule quickly established, and very striking. The two older children (No. 4 and 5) showed during both X-ray and Myleran treatment long-lasting, completely satisfactory remissions. Of the whole course of the disease, 29 and 12 months respectively can be noted as "quiet" periods. Of the three infant children (Nos. 1, 2 and 3), not one showed a completely satisfactory remission. The leucocyte figures were sometimes satisfactorily lowered, while the anemia was never completely cured, and thrombocytopenia persisted most of the time. There was never more than partial disappearance of the splenic enlargement in any of these children even for a short time.

Two of the children were given Colcemid for a period. It was quite obvious that its effect was inferior to that of Myleran.

If any conclusions can be made as regards therapy from this very limited material, they are that in the older children the situation is similar to that in adults, i.e.

that both Myleran and X-ray therapy are two very valuable means of treatment. In the infants, the Myleran effect is probably more difficult to balance, while X-ray therapy has, in these cases also, a satisfactory effect.

As regards acute leukemia in children, there is no doubt that modern methods of treatment give rise to a decided, often very considerable lengthening of the course of the disease. In chronic granulocytic leukemia, irrespective of the age of the patient, it is doubtful whether the therapy lengthens the life expectancy (Wilkinson & Turner, 1959), but it does help the patient to a more tolerable existence, with longer periods of well-being before the commencement of the inevitable, perhaps precipitated terminal phase.

Summary

1. Five cases of chronic granulocytic leukemia in children are reported. Three of the cases were diagnosed during the first year of life, and the two others at $9\frac{9}{12}$ and $11\frac{1}{2}$ years respectively.

2. The clinical picture in the older children was similar to that found in adults. The young children showed a pronounced tendency to infection and an increased tendency to thrombocytopenia and purpura.

3. B_{12} analysis in the serum of untreated cases showed the same greatly raised values as have been observed in adults.

4. The therapy results showed a favourable response to Myleran for the older children, but for the small children its effect was unsatisfactory. X-ray therapy was beneficial for splenic enlargement, leukocytosis and also for local infiltrations and pains, regardless of the age of the child.

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Surgical Treatment of Ulcerative Colitis in Children

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During the past few years, increasing interest has become focused on the treatment of ulcerative colitis. The reasons are evident, i.e., both medical and surgical therapy have become more active, and have led to more satisfactory results than earlier. This can be ascribed to better knowledge and management of the water and electrolyte balance, the introduction of steroid hormones, and more radical surgical measures.

Discussions between physicians and surgeons regarding the indications for surgical intervention have led to much controversy. Thus, some authorities maintain that only 5 to 10 per cent of patients with ulcerative colitis should be operated on (5, 17), whereas others give figures between 20 and 40 per cent (1, 4, 23). The present situation has, in fact, been summed up adequately by the following statement in the *Lancet*, in a review of the International Congress on Gastroenterology (London 1956): ".... (it) ended on a note of high controversy, during which speakers of international repute presented convincing but nevertheless entirely conflicting views".

As a rule, ulcerative colitis has been treated more conservatively in children than in adults (13, 16, 37) and few reports are found on the surgical treatment of patients in the pediatric age groups (12, 16, 20, 25). One of us (R. L.) has earlier given accounts of the medical aspects of the disease in the young (9, 19, 20, 21, 33). The long-term prognosis was found to be unsatisfactory in many cases, and the incidence of cancer was high. An increasing number of our patients have subsequently been operated on. A report is given in the following of our experience in surgical treatment of 23 children and adolescents with ulcerative colitis. On this basis, our discussion is devoted chiefly to the question of whether operation should be performed on children with this disease and, if so, when and what is the method of choice.

Case Material

During the past 9 years, 106 patients with ulcerative colitis have been admitted to the Pediatric Clinic, Karolinska Sjukhuset. Operation was performed on 23 of them: 9 girls and 14 boys (Tables 1 & 2). Their age at the onset of the disease ranged from 3 to 15 years; in only 5 cases did the disease make its appearance before 7 years of age. These tables also show the duration of the disease before operation; it varied from 3 months to 13 years.

All the patients had classical symptoms,

[1] Clinical psychologist.

TABLE 1. *Synopsis of case histories: acute disease.*

Case no.	Sex	Duration yrs	Age at oper. yrs	Indication	Degree of rectal involvement	Type of operation	Complications	Follow-up, yrs	Rehabilitated	State of remaining rectum	Additional surgery
10	M	1	10	Acute, risk of perforation, toxic	Moderate	Colectomy + ileostomy	0	2	+	Improved	0
12	M	3/12	14	Acute	Slight	Colectomy + ileorectal anastomosis	Cicatricial hernia	2	+	Unchanged	Repair of hernia
13	F	2½	13	Acute, risk of perforation	Moderate	Colectomy + ileorectal anastomosis	Fistula, abscesses	2	+	Deteriorated	Sec. proctectomy
14	F	5/12	15	Acute	Slight	Colectomy + ileorectal anastomosis	Intest. obstruct.	2	+	Healed	Laparatomy + lysis
15	F	3/12	12	Acute	Moderate	Colectomy + ileorectal anastomosis	0	1½	+	Deteriorated	0
19	M	7/12	13	Acute, risk of perforation	Moderate	Colectomy + ileorectal anastomosis	Wound rupture	10/12	+	Unchanged	Resuture
20	M	6/12	10	Acute, risk of perforation, toxic.	Severe	Colectomy + ileostomy	0	8/12	+	Unchanged	0

TABLE 2. *Synopsis of case histories: chronic disease.*

Case no.	Sex	Duration, yrs	Age at oper. yrs	Indication	Degree of rectal involvement	Type of operation	Complications	Follow-up, yrs	Rehabilitated	State of remaining rectum	Additional surgery
1	M	2½	14	Chronic, progression	Severe	Colectomy + ileostomy	Wound rupture	7	+	Unchanged	Resuture
2	F	6	15	Chronic, stricture	Severe	Colectomy + ileostomy	Ileostomy dysfunct.	7	+	Deteriorated	1. Revision of ileostomy 2. Sec. proctectomy
3	F	2	14	Chronic, progression	Severe	Colectomy + ileostomy	Intest. obstruct.	6	+	Deteriorated	1. Laparatomy + lysis 2. Sec. proctectomy
4	F	10	16	Chronic, progression	Severe	Colectomy + ileostomy	Intest. obstruct.	5	+	Improved	Laparatomy + lysis
5	F	6	15	Chronic, progression	Moderate	Pancoloproctectomy + ileostomy	Ileostomy dysfunct.	3½	+	—	Revision of ileostomy
6	M	13	16	Chronic	Slight	Colectomy + ileorectal anastomosis	Intest. obstruct.	3	+	Deteriorated	Laparatomy + lysis
7	M	10	14	Chronic, stricture	Slight	Colectomy + ileorectal anastomosis	0	3	+	Deteriorated	0
8	M	8	13	Chronic	Moderate	Colectomy + ileostomy	0	2½	+	Deteriorated	0
9	F	7	10	Chronic	Slight	Colectomy + ileorectal anastomosis	0	2	+	Healed	0
11	M	13	16	Chronic	Moderate	Cclectomy + ileostomy	0	2	+	Unchanged	0
16	M	4	13	Chronic, progression	Severe	Pancoloproctectomy + ileostomy	Intest. obstruct.	1½	+	—	Laparatomy + lysis
17	M	7	14	Chronic	Moderate	Colectomy + ileorectal anastomosis	0	1½	+	Unchanged	0
18	M	8	15	Chronic, stricture	Severe stricture	Pancoloproctectomy + ileostomy	Intest. obstruct. Ileostomy dysfunct.	1	+	—	Laparatomy + lysis Revision of ileostomy
21	F	7	15	Chronic, progression	Severe	Pancoloproctectomy + ileostomy	0	6/12	+	—	0
22	M	5	14	Chronic, progression	Severe	Pancoloproctectomy + ileostomy	0	6/12	+	—	0
23	M	5	17	Chronic	Moderate	Colectomy + ileorectal anastomosis	Intest. obstruct.	4/12	+	Unchanged	Laparatomy + lysis

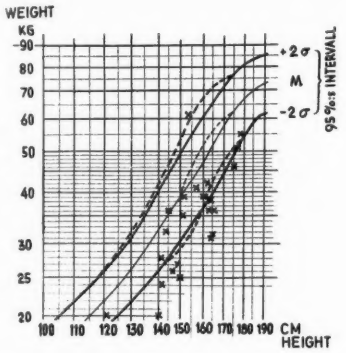

Fig. 1. Patients' weight in relation to height and in comparison to normal variations. *M* = mean of normal. Broken lines = girls when differing from boys. (KARLBERG & IGGBOM: *Acta Pædiat 48*, Suppl. 117, 1959).

i.e., frequent bloody diarrhoea, often at night, weight loss and anemia. Fig. 1 shows the patients' weight before operation in relation to height, as well as in comparison to the normal range. In three cases (Nos. 2, 8 & 20), the height was below the normal variation ($\pm 2.5\ \sigma$). The presence of anemia and/or other extracolonic manifestations is recorded in Table 3.

Repeated fecal cultures for specific organisms, such as *Salmonella*, *Shigella* and dysentery bacilli, were negative. In every case, proctoscopy disclosed signs of proctitis, ranging in severity from slight changes, consisting of swelling and reddening of the mucosa, to granulation and ulcerations (*vide infra* and Tables 1 & 2).

All the patients underwent one or several roentgenologic examinations with barium enema. Pathologic changes in all segments of the colon were demonstrated in every case. The changes were fairly evenly distributed over the whole colon in 16 cases, whereas they were most prominent in the transverse and left part of the colon in the other 7. No fistulas from the colon to adjacent organs were visualized. Reflux of the contrast medium from the colon to the dilated terminal ileum, through a deficient ileocaecal valve of abnormal appearance, occurred in 14 cases. Signs of rectal involvement were present in 13 cases. A more detailed account of the rectal changes from the roentgenologic point of view is given elsewhere in this journal by one of us (U. R.).

In 7 patients (Table 1), the disease had an acute progressive course, with severe impairment of general condition, high fever, serious anemia and marked weight loss. Four of them (Nos. 10, 13, 19 & 20) presented a severe toxic state and roentgenologic signs of impending perforation. Scout films of the abdomen showed marked dilatation of the colon, particularly of the transverse colon and sigmoid (Figs. 2 & 3), as well as free fluid in the abdomen in a few of them. Multiple gas-filled ulcers—evidently submucous or penetrating into deeper layers of the

TABLE 3. *Extracolonic manifestations.*

	Before operation	After operation
Arthralgia, hydrops	7	1
Erythema nodosum	10	1[a]
Stomatitis	4	—
Anemia (hemoglobin < 9 g per 100 ml)	22/23[b]	0/23[b]
Erythrocyturia (Addis count > 4 mill/12 hours)	4/18[b]	0/16[b]
Liver damage (see reference no. 21)	3	0
Eosinophilia (chamber eosinophil count > 300/mm³)	12/20[b]	2/15[b]
Raised gamma globulin ($\geq$ 1.3 g per 100 ml)	18/20[b]	8/18[b]

[a] Before protectomy.
[b] Number positive number investigated.

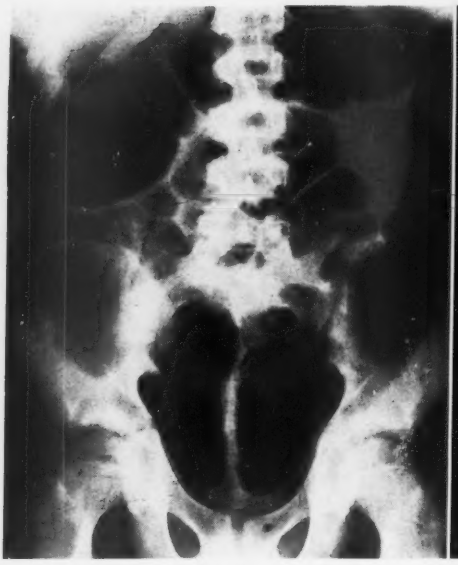

Fig. 2.

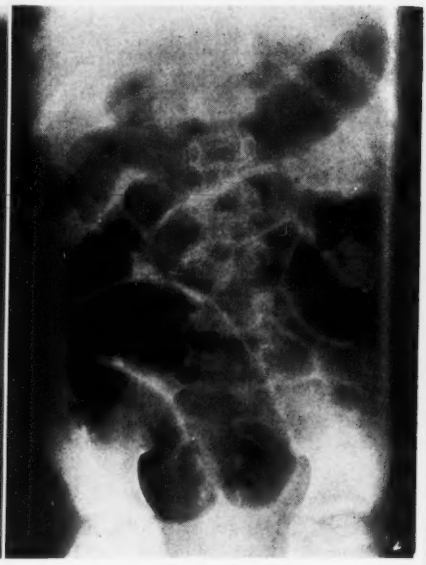

Fig. 3.

Fig. 2. Case 19. A roentgenogram of the abdomen shows distension of the ascending and transverse colon and the sigmoid. Similar changes, although less marked, are present in the distal descending colon. The haustral plicae of the colon are partly preserved. Ulcerations of the descending colon are visible.

Fig. 3. Case 10. A roentgenogram of the abdomen discloses a distended sigmoid colon, as well as dilated small-bowel loops and an increased amount of intraperitoneal fluid. Deep ulcers, distended by gas, are seen in the sigmoid.

wall and undermining the mucosa—were visualized at roentgenologic examination in Cases 10, 12, 15 & 19 (Fig. 4).

The disease was primarily acute, with a duration from 3 to 7 months, in five patients in this group. In the remaining two listed in Table 2 (Nos. 10 & 13), the acute stage represented an exacerbation of a more chronic course, lasting for one and 2½ years, respectively.

In 16 cases (Table 2), the course was chronic and intermittent. Its duration ranged from 2 to 13 years, with repeated exacerbations and more or less complete, long remissions, maximally 6 years. In 9 patients, the course was markedly progressive.

All patients with chronic disease were partly or completely disabled for long periods. During lengthy exacerbations they were tired, often depressed, and were never able to be far from a lavatory. As a result, they could not, for example, mix freely with their comrades or join in sports. In all but two cases, their disease necessitated absence from school to such an extent that they had to repeat one or more classes. One girl (Case 9) was hospitalized 18 times, and the other patients from 5 to 11 times. The menarche had not yet appeared in two girls aged 15 and 16, respectively. In five cases (Nos. 1, 3, 16, 22 & 23), the disease was of shorter duration (2 to 5 years); the manifestations were more pronounced and continuous, and the disability more severe.

At roentgenologic examination shortly before operation, the distensibility of the colon was often decreased in cases with a slowly progressive or chronically remittent course. This feature was marked in five cases, and moderately pronounced in two. The reduced

Fig. 4.

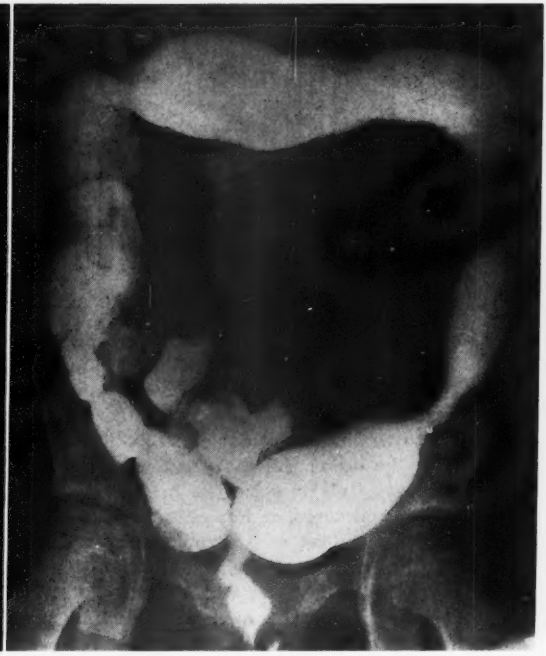

Fig. 5.

Fig. 4. Case 10. At barium enema examination, deep ulcerations of the descending colon are visible.

Fig. 5. Case 2. Shortened colon with retracted flexures and reduced distensibility. Strictures are present in the right flexure, descending colon, sigmoid and rectum. Complete loss of haustra. The surface pattern is irregular. In the original film, thickening of the colonic wall can be discerned.

capacity was reflected in shortening of the colon, with a varying degree of retraction of its flexures and a decrease in its transverse diameter. In several of these cases, thickening of the colonic wall was visible on the roentgenogram. Strictures were demonstrated in four cases; in two (Nos. 2 & 7) they were multiple (Fig. 5), and in two (Nos. 1 & 11) isolated.

An investigation of all the patients was made by our team of child psychiatrists (Physician-in-Chief: Dr. E. B. Nordlund). In no case did it disclose any psychologic factors considered to be of etiologic importance in the patient's disease.

Morbid Anatomy

Gross

Signs of peritoneal irritation were a common finding at laparotomy, especially in the acute cases. Thus, an increased amount of turbid fluid was present in 6 out of 7 acute cases, as compared to 5 of 16 chronic cases. A network of small vessels covering the serous surface of the diseased part of the bowel was a fairly constant finding. The colon was contracted, i.e., shortened and thickened. Pericolitis was present in all the acute cases, and in 10 of the 16 chronic ones. Widespread, marked enlargement of lymph nodes in the mesentery, mesocolon and mesorectum was a characteristic feature. The

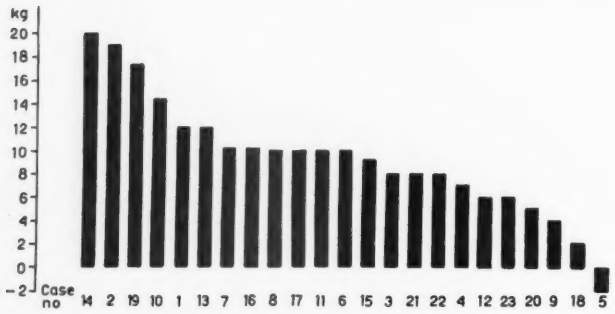

Fig. 6. Weight gain during the first 6 months after operation.

external lesions were, however, moderate in comparison to the internal ones in the excised part of the bowel. All the specimens presented the typical gross lesions, in the form of ulcers and more or less extensive mucosal atrophy or loss, with granulations and, in 11 cases, pseudopolyposis.

The length of colon involved was found to be in agreement with the roentgenologic observations. In all but one patient (No. 15) the distal ileum showed slight or moderate hyperemia, and infiltration extending for maximally 50 cm.

Every excised specimen was sectioned, and submitted to a thorough microscopic examination. The histologic changes were of the type usually seen in ulcerative colitis, consisting of non-specific inflammation and ulcers. No signs of specific inflammation or malignancy were observed. Neither periarteritis, fibroid necrosis, giant cells nor epithelioid cells were present.

The degree of rectal involvement can be inferred from Tables 1 & 2. No fistula was present in any of the cases.

Medical Treatment

Initially, all the patients were treated medically, whenever possible as out-patients. Diarrhoea was not, *per se*, regarded as an indication for bed-rest. The patients were allowed to attend school, and encouraged to take part in other activities up to the limit of their capacity. Most of them were given a mixed, appetizing diet with a high protein content, and composed with regard to individual idiosyncrasies. All were treated with salicylazosulphapyridine (Azulfidine, Pharmacia) for long periods. In addition, all but three (Nos. 2, 3 & 21) were given ACTH or adrenocortical steroids, parenterally and/or by mouth, but in some cases as a rectal drip as well. One patient (No. 2) was under psychiatric treatment, in the form of psychoanalysis, for 3 years; the others were given supportive psychotherapy, as a rule by the pediatrician in charge. Blood transfusions and/or iron medication were given in every case. Apart from the 7 acute cases, all the patients under medical treatment showed some degree of improvement during a varying period.

The indications for operation can be inferred from the aforegoing account of the case material and from Tables 1 & 2.

Surgical Treatment

Preoperative Treatment

Severe anemia and disturbances in fluid and electrolyte balance were corrected. This treatment was continued during and after operation. In the chronic cases in which corticosteroids were administered, operation was postponed for at least a month after discontinuing therapy. In the

acute cases, the dose was increased in connexion with operation, after which therapy was gradually discontinued. Colonic irrigations were not given preoperatively, nor was the intake of solids or fluids restricted for any lengthy period. Terramycin was administered to all the patients for 2 days before operation, as well as 2–3 days after it.

Surgical Technique

Total colectomy and ileostomy in one stage were performed in 13 cases (Nos. 1–5, 8, 10, 11, 16, 18 & 20–22). In 5 of them (Nos. 5, 16, 18, 21 & 22), excision of the rectum was done at the same time. Ileostomy was performed according to the principles recommended by Lahey (22) and Brooke (7).

In the remaining 10 cases (Nos. 6, 7, 9, 12–15, 17, 19 & 23). operation consisted of total colectomy with ileorectal anastomosis, in the first 3 cases with a temporary defunctioning ileostomy according to Aylett (2) and in the others without it.

Our choice of surgical technique was based on the state of the rectum as shown by proctoscopy, barium enema and laparotomy findings.

In the 10 cases in which the rectal lesions were mild, an ileorectal anastomosis was created, whereas primary excision of the rectum was performed when the lesions were severe. Finally, when the lesions of the rectum were of moderate degree, it was spared for possible future closure of the ileostomy, and restoration of bowel continuity by ileorectal anastomosis.

Postoperative Course

The postoperative reaction was surprisingly mild in every case, including those in which emergency operation was performed. Blood loss during operation, including estimated intracolonic blood, was amply substituted. A nasogastric tube was used routinely for decompression until bowel movements started. Fluid loss through the gastric tube, and later through the ileostomy or rectum, was measured and replaced by adequate electrolyte solutions. As a rule, the total losses were considerable and sometimes remarkable during the first postoperative week. With careful attention, no serious difficulties were, however, encountered in meeting the demands for adequate replacement.

Apart from the complications listed below, convalescence was rapid and uneventful. No death occurred in this series, and all the patients were discharged in good condition.

The surgical complications which occurred are recorded in Tables 1 and 2, and can be summarized as follows:

	No. of cases
Wound rupture	2
Cicatricial hernia	1
Small-bowel obstruction	
Early	2
Late	5
Ileostomy dysfunction	5

Intestinal obstruction due to adhesions developed early in two cases (Nos. 14 & 23), i.e., after one week and two weeks, respectively. In the other cases (Nos. 3, 4, 6, 16 & 18), obstruction occurred later (in Case 18 twice), i.e., from 1 to 21 months after operation. In every case, obstruction was relieved by laparotomy and lysis of adhesions.

Ileostomy trouble appeared in 5 of 13 cases. Two patients (Cases 2 & 18) had signs of obstruction, due to stricture of the

stoma. The symptoms subsided after revision of the ileostomy. Perforation of the ileostomy occurred in two cases; revision of the ileostomy was done in one of them (Case 1). In the other (Case 4) secondary ileorectal anastomosis is planned for the near future, thus eliminating the ileostomy. Disturbing sounds came from the stoma in Case 5; at revision, subcutaneous dilatation of the terminal ileum was detected and removed.

Additional surgery for treatment of the primary disease was required in two patients (Cases 2 & 3) in whom the rectum had been left *in situ* at primary colectomy with ileostomy, and in one (Case 13) after ileorectal anastomosis. In view of persistent or progressive proctitis, excision of the rectum was performed in all three patients. This was done 7 years, 10 months and 2 years, respectively, after the primary intervention.

Follow-up Studies

After operation, all the patients were kept under continuous observation, five for 4 to 8 years, twelve for 2 to 3 years, and two for 1 year; the remaining four were operated on about 6 months before the time of writing (Tables 1 & 2).

Patients' Appraisal of their condition

The patients, as well as their parents, have considered the operation to have resulted in considerable, steady improvement. Strength, spirits, sleep and appetite have become much better. The patients have been able to manage their school work or job with far greater ease. They have joined in the same activities as their comrades; they play football and ice-hockey, go skiing and take part in gymnastics and swimming. Most patients mix with their comrades to a greater extent than formerly. Most of the girls and some of the boys go dancing. The oldest female patient with a permanent ileostomy is now 22 years old, and has normal sexual relations.

The patients state that they can tolerate a much more varied diet than before operation. Most of them eat the same food as the rest of the family. They emphasize the fact that they are no longer dependent on always being close to a lavatory. All the patients—including those with an ileostomy—definitely prefer their present condition to that before operation. They do not feel the ileostomy to be any serious drawback.

Objective Appraisal of the Patients' Condition

All the patients are alive, and their general condition has improved. The gain in weight during the first 6 months after operation was considerable, and often dramatic, as can be inferred from Fig. 6. Their physical development subsequently became adjusted to normal proportions, and at follow-up examination all were within the normal range.

Except in one case (No. 20), no anemia was present after operation. A delayed menarche occurred in two girls during the first year after operation, and their menstruation has been normal since then. All the patients have attended school or worked without undue absence. Extracolonic manifestations have been infrequent (Table 3).[1] Eosinophilia and raised gamma globulin have been recorded in a few patients, but only in those with the rectum

[1] Arthritis in a girl with ileorectal anastomosis.

in situ, or with a perineal fistula after proctectomy (Table 3).

Bowel Function

Most of the patients with an ileostomy manage their bags themselves. They change the bag 2–4 times a day, and seldom during the night. The stools are generally in the form of a thick fluid, sometimes semi-solid, and have varied with the food eaten. Most patients prefer the stools to be slightly loose. As a rule, there has been no meteorism, smell, or bubbling in the stoma. Irritation of the skin has been prevented effectively by the use of ointments.

The patients with an ileorectal anastomosis generally have from two to six bowel movements a day, and only rarely in the night. None of them have been incontinent or had an imperious need to defecate. The stools are usually semi-solid, of the consistency of porridge, but are sometimes formed, especially in the morning.

State of Remaining Rectum

In 2 of the 10 cases in which ileorectal anastomosis was performed (Tables 1 & 2), postoperative proctoscopy showed total regression of the slight lesions present earlier. Barium enema examination of these two patients (Cases 9 & 14) showed no pathologic rectal features either before or after operation. In four cases (Nos. 12, 17, 19 & 23), follow-up proctoscopy disclosed persistent, slight or moderate proctitis, although no changes were observed at either pre- or postoperative roentgenologic examination. The remaining four patients in this group (Cases 6, 7, 13 & 15) showed slight or moderate progression of proctitis, both at proctoscopy and at barium enema examination. In one of them (Case 13), perineal and vulvar abscesses and fistulas developed after operation, necessitating secondary proctectomy and ileostomy 2 years after the primary intervention. All the patients in this group have done well and have had no complaints, irrespective of the local conditions in the rectum observed at follow-up examination.

Two (Cases 4 & 11) of the 8 patients who underwent primary colectomy and ileostomy, the rectum being preserved, showed marked regression of proctitis 5 and 2 years, respectively, after operation. In three cases (Nos. 1, 11 & 20), the degree of proctitis was relatively unchanged. In the remaining three cases (Nos. 2, 3 & 8), progressive changes occurred. At the time of writing, secondary proctectomy has been performed in two of them (Cases 2 & 3), 7 years and 10 months respectively, after the primary operation.

Psychologic Studies

A psychologic study of 13 patients was made by one of us (L.B.). In most cases it took place about 1 year after operation, but in a few cases not until about 4 years after it. The investigation consisted of interviews, as well as projective tests (TAT), the latter intended to uncover deep-seated traits.

During the interviews, the boys were polite, outwardly easy to contact, anxious to please and to appear well-adjusted. Underlying this attitude they were, however, characterized by insecurity, lack of initiative, depression, suspicion and a feeling of being misunderstood. They were unduly dependent and childish, and had an abnormally great need of support and

encouragement. They were unwilling to become involved emotionally, for fear of being disappointed. With respect to sexual relations, for example, they seemed to try to mask this attitude by a pretended lack of knowledge. They had little capacity for empathy.

The girls were similarly docile and pleasant. They frequently had a superficially optimistic attitude, which did not seem to be compatible with their underlying emotional experiences. They were nevertheless better adjusted than the boys. Basically, they were less passive than the boys, although it was evident that their attitude to life was also cautiously expectant. Their vitality was fairly low, and they were uncommonly little aggressive or critical. They condemned aggressiveness as immoral. One 16-year-old girl (Case 14) with a relatively short preoperative history differed from the others, her current state being characterized by an explosive, uninhibited puberty.

The patients had relatively few contacts with their comrades but, in this respect as well, the girls were better adjusted than the boys. None of the patients had a tendency to isolate themselves, but they were seldom particularly active.

Their attitude to sexual affairs was generally cool and impersonal. All the boys except the oldest one (Case 6) denied having any interest in the opposite sex. As far as relations with their parents were concerned, they were characterized in the boys by antagonism to the father. This was sometimes so frustrating that it prevented normal contact and bonds with other people, such as the mother, friends and girls. The attitude of the girls to their mother was not as negative.

The emotional development and current emotional state were in good agreement with the observations made in the patients before operation, as well as in other patients with a long history of ulcerative colitis.

Discussion

Has surgery a place in the treatment of ulcerative colitis in childhood?

Unsatisfactory long-term results of medical treatment in many of our patients motivated our introduction of surgical treatment in 1953. Gratifying results in our first patients, as well as accumulating evidence of low mortality and excellent results in adults, have encouraged us to widen our indications for surgery.

We have operated on 23 out of a total 106 patients with ulcerative colitis. Six of them were, however, referred to us for operation from other hospitals. The operative rate in our own series therefore amounts to about 17 per cent. This rate is certainly compatible with recent figures in adult series, but is probably high for a series of children. We have been unable to find any reports of surgical treatment in large pediatric series.[1]

The results of surgical treatment have been satisfactory in our series. Long-standing illness or an acute life-threatening condition has been replaced by a state of health and adaptation to normal life. Bowel function has become adequate, accompanied by a conspicuous, rapid gain in weight and normalization of blood values. Extracolonic manifestations, com-

[1] Following completion of this paper Platt, Schlesinger & Benson published data in accord with our findings (*Quart J Med 29:* 257, 1960).

mon before operation, have been few and slight after it. The physician in our team (R.L.)—who has had numerous patients under continuous observation for many years—has been particularly impressed by the striking improvement in the surgical cases as compared to that in the medical ones. Although remissions are common in ulcerative colitis, they are rarely as complete, or of such long duration, as in the cases treated by surgery. It is true that postoperative complications were frequent, but they were transient and, so far, amenable to surgical correction. We are, however, fully aware of the short follow-up period in a number of our patients.

Indications for Surgery

On the basis of our present experience, we consider the indications for surgical treatment to be as follows:

Absolute indications

(1) Perforation or risk of perforation, stricture, profuse hemorrhage, cancer.

(2) Fulminating, life-threatening disease not promptly improved by medical treatment.

Relative indications

(3) Total disablement for more than 1 year, despite medical treatment.

(4) Partial disablement for more than 5 years, despite medical treatment. Retarded development. Risk of cancer.

Opinions are in agreement regarding the validity of the absolute indications. It has been shown by several investigations that roentgenologic examination is often of particular value in the acute, fulminating cases (18, 24, 26, 27, 28, 30, 34, 40). Thus, when it shows a greatly distended colon with a thin wall, it provides an additional strong argument in favour of operation, since perforation must be regarded as imminent. This was found to apply in our cases.

We consider that surgical intervention should be considered in children and young adults who—despite medical treatment—have been totally disabled by their illness for more than a year. The indications should obviously be stricter in the presence of milder disease, with less effect on the general condition and functional capacity. Some authorities maintain that 80–90 per cent of patients with ulcerative colitis of this type are cured or improved by medical therapy (5, 17, 37). Others—especially surgeons—are of the opinion that many of these patients are nor sufficiently improved and, at any rate, not rehabilitated (1, 4, 7, 23, 32). We share the view that many patients with ulcerative colitis actually suffer more than either they themselves or their doctors are willing to admit. Many patients, in fact, dissimulate—as pointed out earlier by Alm & Ihre (1).

Psychologic studies were made in only about half our patients, and could not be carried out as continuously as the other investigations. Moreover, the projective tests used have a limited validity (14). Consequently, any conclusions regarding the mental state of the patients in relation to operation must be drawn with caution. It is, however, noteworthy that we found most of the patients to be superficially well-adapted and harmonic, whereas underlying this they were characterized by emotional immaturity, lack of initiative, insecurity and an abnormally great need

of support and encouragement. Such a discrepancy between the superficial attitude and the deep-seated psychologic traits has been stressed as chaacteristic of patients with ulcerative colitis (10, 36). Our patients did not, on the other hand, exhibit any obsessive traits, which have been stated by other authors to be typical (10). Sexually, our patients seemed to be retarded.

The characteristic personality traits seem to be less dependent on a traumatic experience or the patient's current situation (e.g. operation or ileostomy) than on the personality development prior to operation. It is, in fact, conceivable that the great effect on emotional development —which was common in our series—should be regarded as an additional indication for operation. Operation at an earlier stage might have led to normal maturation.

Surgical treatment should be deliberated when the disease has been present for 5 to 10 years, and medical therapy has been unable to prevent lengthy exacerbations and an unfavourable effect on the patient's general condition, growth and adjustment. If more than 10 years have elapsed since the onset, operation should be undertaken—even if the manifestations have not been so severe or constant—partly in view of the risk of cancer.

It is our firm belief that indications for surgical treatment should be more liberal in children than in adults. This attitude is based on the following considerations.

It is evident that the growing organism suffers more from a chronic disease than does the adult one. Signs of physical and emotional retardation were common in our series. Surgical treatment seems to offer the best possibility at present available for promoting normal development and adjustment. The risk of malignancy—the most dreaded late complication—is greater when the disease has its onset in childhood (12, 33, 39). In ulcerative colitis, cancer may appear after many years' remission, and is exceedingly difficult to diagnose and to treat successfully (4, 12, 33). These dangers strengthen the relative indications for operation when the duration of the disease has been long, i.e., more than 10 years.

The decisive arguments are, however, the degree of destructive lesions as seen in the excised specimens, as well as the dramatic improvement that has followed surgery.

Choice of Operation

Today, temporary ileostomy alone has been abandoned by most surgeons in the treatment of ulcerative colitis. All evidence points to the necessity of more radical procedures. It is obvious that radical excision of the entire diseased part of the bowel, with restoration of bowel continuity, is the ideal method of surgical treatment. Unfortunately, in most cases the extent of the pathologic process does not allow both these prerequisites to be fulfilled. Segmental colitis is rare, and the rectum is unanimously stated to be involved in 90–95 per cent of all cases. These facts force the surgeon to renounce one of his two ideal requirements—either radicality or bowel continuity. The choice is not an easy one. Most surgeons with experience in this field prefer radical excision (pancoloproctectomy) combined with permanent ileostomy (4, 7, 11, 29).

A few authorities have insisted on restoration of bowel continuity, either by ileo-anal or ileorectal anastomosis. Ileo-anal anastomosis has been done in relatively few cases of ulcerative colitis (6, 12, 31). The results have been disappointing, and today this procedure seems to have been abandoned even by Ravitch [Burt (8)]. Ileorectal anastomosis has, on the contrary, been performed in large series, with surprisingly good results even in the presence of severe proctitis. Aylett (2, 3) has been one of the foremost advocates of this procedure. In his personal series of 135 cases, the overall mortality was 5.4 per cent, full rehabilitation being achieved in 90 per cent of the patients. Aylett stated that regression and healing of proctitits were common after operation. Secondary excision of the rectum and ileostomy were necessary in only four cases.

When dealing with the specific age groups of childhood and adolescence, the desire to preserve bowel continuity is naturally greater than in adult practice. Most parents and children have a strong prejudice against permanent ileostomy. This has not failed to influence our approach to the problem.

Our selection of surgical procedure has been a compromise between radical excision and preservation of bowel continuity. The fact that primary ileorectal anastomosis was performed in 10 of 23 cases (43.5 per cent) suggests that we have often compromised with radicality in our series. At proctoscopy, all these patients had in fact, signs of slight or moderate proctitis. In 8 of these cases, no signs of rectal involvement were, however, observed at roentgenologic examination. This indicated that the inflammatory lesions were superficial, and helped us in selecting these cases for ileorectal anastomosis. The gratifying results so far seem to corroborate Aylett's statement, i.e., they show that proctitis may subside after ileorectal anastomosis and, if it persists, has no major bearing on the patient's well-being. Regular follow-up examinations by proctoscopy and barium enema are, however, mandatory in these patients, in view of the risk of malignancy.

Total colectomy and ileostomy, with closure and preservation of the rectum, were performed in 8 cases. In these patients, the degree of rectal involvement was considered to make them unsuitable for primary anastomosis, but not necessarily to rule out the possibility that the proctitis would heal after removal of the diseased colon. This decision has been justified in so far as marked regression of proctitis has occurred in two cases. Secondary closure of the ileostomy and ileorectal anastomosis are being considered in these patients. In two cases, secondary proctectomy has already been done, and will probably be performed in the near future in the other four cases.

In the long run, it seems inadvisable to leave the closed rectum in place. If improvement or healing of proctitis occurs, bowel continuity should be re-established. If proctitis is progressive or persistent, the rectum should be removed, since it may become the site of a malignant process. An additional reason for proctectomy is the established fact that proctoscopy may be an extremely painful procedure in the presence of an inflamed and contracted rectum. These patients will soon omit attendance for regular follow-up examinations, and thus deprive themselves of the

possibility of early detection of a malignant growth.

Primary pancoloproctectomy was performed in only 5 of our cases. The severity of rectal involvement was the reason for this choice. From the surgical point of view, there were clear-cut indications in these patients for removal of all diseased bowel, renouncing the desirable restoration of bowel continuity. The results in this group have amply justified the radical procedure. As expected, complete eradication of the disease was achieved in evey case. Adjustment to ileostomy life has been surprisingly good, in view of what could have been anticipated in this low age group. We had been prepared for the patients with an ileostomy to have greater emotional disturbances than those with an ileorectal anastomosis, but this did not prove to be the case. Both groups showed about the same emotional characteristics, and the same good social adjustment. We have, in fact, found that the best way to convince a new candidate, as well as his family, of the benefits of ileostomy and pancoloproctectomy is to introduce them to one of our earlier ileostomy patients.

Whether these radical procedures should be performed in one, two or even three stages is the subject of controversy. We have preferred to complete the whole operation in one stage, and our results so far seem to justify our choice.

Summing up our experience of the different surgical procedures, it seems that they all have a definite place in the treatment of ulcerative colitis. In children at any rate, ileorectal anastomosis should be the first choice in the absence of severe proctitis, rectal stricture and rectal fistulas.

The borderlines between slight, moderate and severe proctitis are evidently ill-defined and fairly subjective. When there is any doubt regarding the degree of proctitis, it seems advisable to leave the rectum *in situ* at the primary operation. Its condition should then be assessed at regular intervals, for as long as may be required to determine whether it should be removed, or whether bowel continuity should be restored.

In the presence of definitely severe proctitis, pancoloproctectomy should be performed. Both the patient and his parents should be reassured that adjustment to ileostomy life will take place.

Our only disappointment associated with surgical treatment has been the high incidence of complications, particularly of small-bowel obstruction. Our experience is in agreement with that reported in most series. No definite difference was observed between the incidence of complications following the three procedures used in our series. There are two obvious explanations of the common occurrence of postoperative intestinal obstruction, i.e., the large denuded areas left after colectomy, and the inflammatory lesions in the operative field, especially in the mesenteric lymph nodes. At the present time, no reliable means seem to exist for prevention of these complications.

Summary

Radical surgery has been performed in 23 children and adolescents with ulcerative colitis. This implies that about 17 per cent of the patients at the Pediatric Clinic, Karolinska Sjukhuset, with this disease were operated on. The clinical, roentgenologic and psychologic features, as well as

the morbid anatomy and surgical methods, are described and discussed. Particular interest is focused on the indications for operation and the choice of surgical method. It is stressed that the indications for surgical treatment of ulcerative colitis should be more liberal in growing patients than in adults. The detrimental effect of the disease on the physical and emotional development of children and adolescents, as observed in the present series, would presumably be counteracted by operation, provided that it is performed in time.

No death occurred in this series. All the patients improved rapidly after operation. An acute life-threatening condition, or a chronic disabling disease, has been replaced by a state of health and functional fitness. The patients with an ileostomy are well-adjusted. The follow-up period has ranged from 6 months to 8 years.

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Chronic Supraventricular Tachycardia of Continuous or Repetitive Type in Children

A Note on Circulatory Function and Long-Term Prognosis

by GUNNAR STRÖM, ERIK ZETTERQVIST and PER ZETTERQVIST

Chronic supraventricular tachycardia is an unusual disturbance which may occur also in children. In such cases, signs of gross congenital malformation or acquired disease of the heart are usually absent, and the condition may be so stable over a period of many years that a local malformation of the impulse-forming atrial or nodal system has been suggested as its cause (Parkinson & Papp (7)). The tachycardia may be either of a "continuous" and "constant" type or of a "repetitive" and "paroxysmal" type, and it is clearly distinguished from the classical paroxysmal atrial tachycardia.

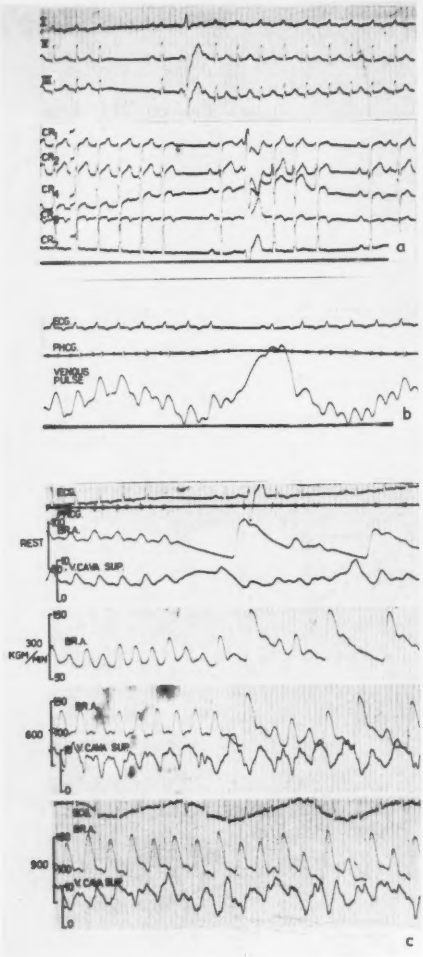
The circulatory functional effect of the supraventricular tachycardia appears to depend partly on the degree of atrioventricular (AV) conduction block, i.e. on the resulting ventricular rate, and partly on the effectiveness of ventricular contraction at these high rates. In the majority of pediatric cases, no serious incapacitation is produced or there may even be no subjective symptoms at all. The long-term prognosis is judged to be good, at least in children, in whom spontaneous remission often occurs in adolescence (see Parkinson & Papp for literature). Therapy is usually ineffective.

However, a favourable outcome of the disturbance cannot be assured in every case of the "repetitive" type (cf. 2, 4), and the prognosis in cases of the 'continuous' type may also be uncertain (cf. 1, 3, 5, 6, 8). It therefore seems justifiable to report four cases of chronic tachycardia which we have followed for a considerable length of time as they give additional information about the disturbance, its effect on circulatory function and its clinical course.

Case reports

CASE 1. Male patient O.S., born May 1, 1935. In 1938 uncomplicated scarlet fever. In 1940 tonsillectomy. In 1941 erythema nodosum and enlarged hilar lymph glands, subfebrile, morning pulse rate 70–90 beats/min. In 1944 arrhythmia was first noted, at routine medical examination.

In 1949 irregular tachycardia was observed, otherwise normal physical findings. Electrocardiography (Dr. T. Möller, Kronprinsessan Lovisas Barnsjukhus) showed chronic atrial tachycardia of periodic type, consisting of periods of a few, up to 20–30 rapid beats of ectopic atrial origin (rate 120–140 beats/min) interrupted by one or a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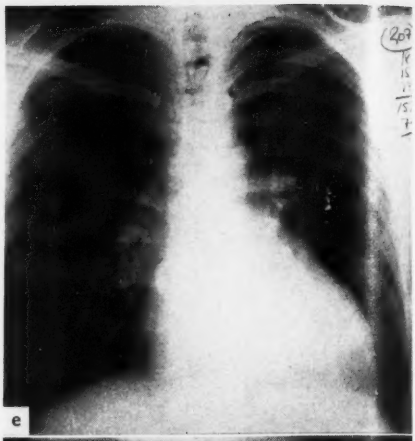
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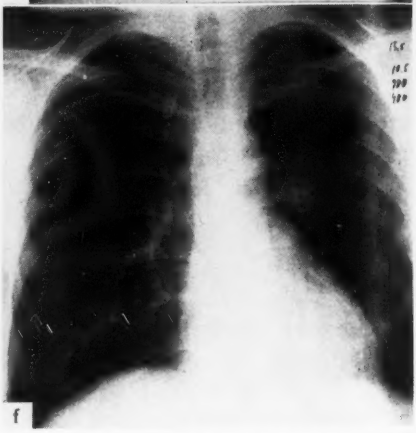
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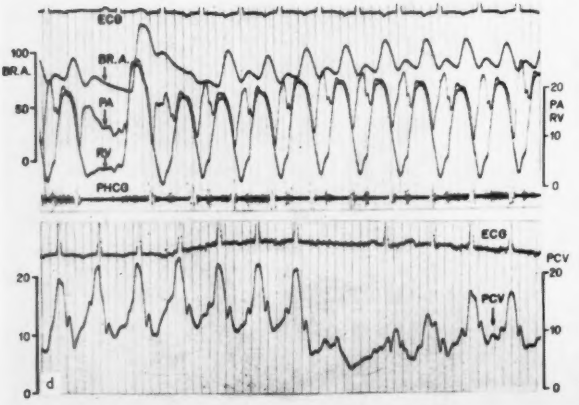
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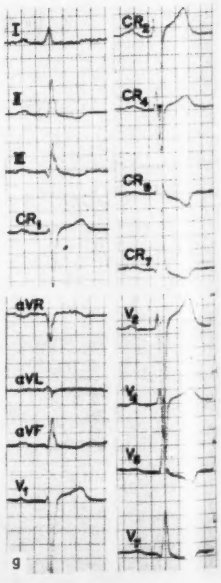
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few normal sinus beats. The ectopic beats sometimes showed aberrant intraventricular conduction and usually ended by AV conduction block (see Fig. 1, 2). Otherwise the ventricular complexes were normal.

The arrhythmia persisted unaltered from 1949 onwards but the patient experienced no subjective discomfort and led a normal life, including participation in light sports. In 1955, during military service, he was admitted to Karolinska sjukhuset for control examination. The tachycardia persisted, and the apex beat had now become broad and lifting. Auscultation was difficult to interpret. Phonocardiography at rest showed, in the normal beats, normal first and second sounds (Fig. 1*b*), a high-frequency fourth sound along the left sternal border which became apparent in long diastolic intervals, and a slight systolic ejection murmur over the pulmonary area. During a period of tachycardia, mechanical systole had a duration of 0.25 sec, diastole 0.12 sec. Electrocardiography showed a relatively high QRS voltage and slightly inverted T-waves over the left precordium (Fig. 1*a*). Right-heart catheterization: at rest average heart rate 125, average stroke volume 78 ml, arteriovenous (A–V) O_2 difference 39 ml/l, pressures in right atrium 2 mm Hg, right ventricle 22/6, pulmonary artery 21/17, pulmonary wedge position 11, brachial artery 118/85; during work of 300 kpm/min heart rate 125, stroke volume 94 ml, A–V O_2 difference 83 ml/l; during work of 600 kpm/min heart rate 140, average stroke volume 104 ml, A–V O_2 difference 98 ml/l, pressures in right atrium 5 mm Hg, right ventricle 40, pulmonary artery 37/22. The pulmonary wedge-pressure curve showed relatively high atrial peaks (Fig. 1*d*). During the course of a period of tachycardia, the pressure in the right atrium and superior vena cava usually showed a slight fall, while the pressure in the pulmonary artery and the pulmonary wedge position (reflecting the left atrium) showed a moderate increase. At rest, the pressure in the brachial artery showed large fluctuations (115/70–85/75), with a low pulse pressure during a period of tachycardia. During muscular work of increasing intensity, the heart rate became more and more regular and the pulse waves more constant in appearance (Fig. 1*c*). Roentgenography showed a normal configuration of the heart but there was a conspicuous general enlargement out of proportion to body size, blood volume and resting cardiac stroke volume. During sleep, a 2:1 AV block was registered, resulting in a normal ventricular rate. Quinidine and procainamide in full dosage did not influence the arrhythmia. After high doses of intravenous Lanatosid C, a constant 2:1 AV block of the rapid ectopic impulse was produced. As this effect was believed to be beneficial, the patient was kept on a daily dose of 0.2 mg of digitoxin for long periods (Febr. 26–Oct. 1, 1956, and from June 5, 1958, onwards, see Table 1). During the first period of digitoxin medication, the bouts of tachycardia became shorter, usually showing 2:1 AV block, and after the end of muscular exercise, there often occurred periods of regular sinus rhythm. The heart volume decreased considerably, and the hemoglobin concentration in peripheral blood decreased moderately (see Table 1). The average heart rate during work was lower at any work load than before digitalis medication. During the following one and a half year, digitoxin was not given. The heart volume then increased considerably, the he-

Fig. 1. Case 1, male patient O.S., born 1935. Repetitive paroxysms of supraventricular tachycardia, occurring in close sequence, with periodic AV block. (*a*) Standard and precordial ECG leads, showing pauses between paroxysms of different duration (1955); (*b*) ECG recording with phonocardiogram from 4th L.I.S. and venous pulse registered from external jugular vein (*c*) Heart catheterization study: pressures in superior vena cava and brachial artery at rest and during work of specified intensities; (*d*) Heart catheterization study: pressures in right ventricle, pulmonary artery, and pulmonary wedge position (PCV) at rest; (*e*) Chest roentgenogram in May 1958, without digitalis therapy, heart volume 1520 ml; (*f*) Chest roentgenogram in May 1958 with digitalis therapy, heart volume 980 ml; (*g*) Complete ECG recording (1958), showing signs of left-ventricular hypertrophy. Time marking: distance between vertical lines = 0.1 sec.

moglobin concentration increased moderately, and the heart rate at comparable work loads increased. When digitoxin was given again, heart volume, hemoglobin concentration and heart rates at rest and during work decreased once more. When, at the latest examination, the rhythm had become essentially normal (Fig. 1*g*), a considerable further decrease had taken place. Now the heart-rate response to the graded work test also showed a linear rise with the work load, as is normally the case. The patient was still subjectively healthy. He himself had noted that the heart had resumed a regular rhythm. Electrocardiography (Fig. 1*d*) showed in the left precordial leads a high QRS voltage, an increased left ventricular activation time, S–T depression and inversion of the T waves, suggestive of left ventricular hypertrophy.

Case 2. Male patient A.E. born Febr. 3, 1947. Cardiac arrhythmia was detected at the age of 5 years. He had episodes of tachycardia, mostly in connection with exercise but a few times each year without any known provoking factor. On the last-mentioned occasions he was confined to bed for one or two days because of palpitations, tiredness, nausea, vomiting, and anorexia. During a few weeks prior to the first appearance of these symptoms, the boy had been a little tired and irritable but subsequently he was quite free of symptoms between the attacks of tachycardia. He took part in school gymnastics but avoided too strenuous efforts.

About 6 weeks after the first appearance of symptoms the boy was admitted to the local hospital. Physical examination revealed nothing of pathological significance except the arrhythmia. Routine laboratory investigations including ESR, BMR and AST gave normal results. During the first few weeks the boy had a regular atrial tachycardia of the type described below with every atrial impulse conducted to the ventricles. Pressure on the eyeballs caused inhibition of single ventricular beats, and after injection of Neostigmin a Wenckebach periodicity of AV conduction was observed without any change in the atrial tachycardia. Quinidine treatment produced normal sinus rhythm but had to be interrupted after about 10 days as the patient developed allergic and toxic symptoms (exanthema, and tachycardia with broad ventricular complexes). However, a spontaneous tendency to a second degree AV block later appeared. Digitalis seemed to increase this block, thus diminishing the ventricular rate, and treatment with moderate doses was continued during the following two years. Finally it was discontinued, as the effect was now not significant and as the patient mostly had no symptoms even without medication.

In the autumn of 1958 he was admitted to the Pediatric Clinic, Karolinska sjukhuset.

Clinical examination. Normally developed, somewhat slender youngster in a good general condition, physically active, intellectually well developed without "nervous" symptoms. Heart findings quite normal except variations in the rhythm. During complete rest the ventricular rhythm was regular at a frequency of about 90 beats/min. During slight activity a bigeminy was often found. Sometimes, in connection with effort or after long-lasting standing or walking, a tachycardia with a frequency of 200–250 beats/min appeared. No venous pulses were visible. Roentgen examination of heart and lungs as well as routine laboratory investigations, including electrolyte studies, NPN, WR and thyroid function tests, were not remarkable.

ECG studies (Fig. 2). The ECG was followed for 7 years. Except for a short period of sinus rhythm, mentioned above, it always showed a regular ectopic atrial tachycardia. The P-waves were always of the same type, though varying in frequency. At rest this was about 180 impulses/min. During moderate activity, after prolonged standing, and during the exercise tolerance test it increased successively with a maximum of 265 per minute, without paroxysmal changes. A partial AV block of a variable type, probably due to a Wenckebach mechanism, was also present: at rest a 2:1 block with prolonged AV conduction time; at other times a Wenckebach periodicity with periods of 3–20 consecutive impulses transmitted to the ven-

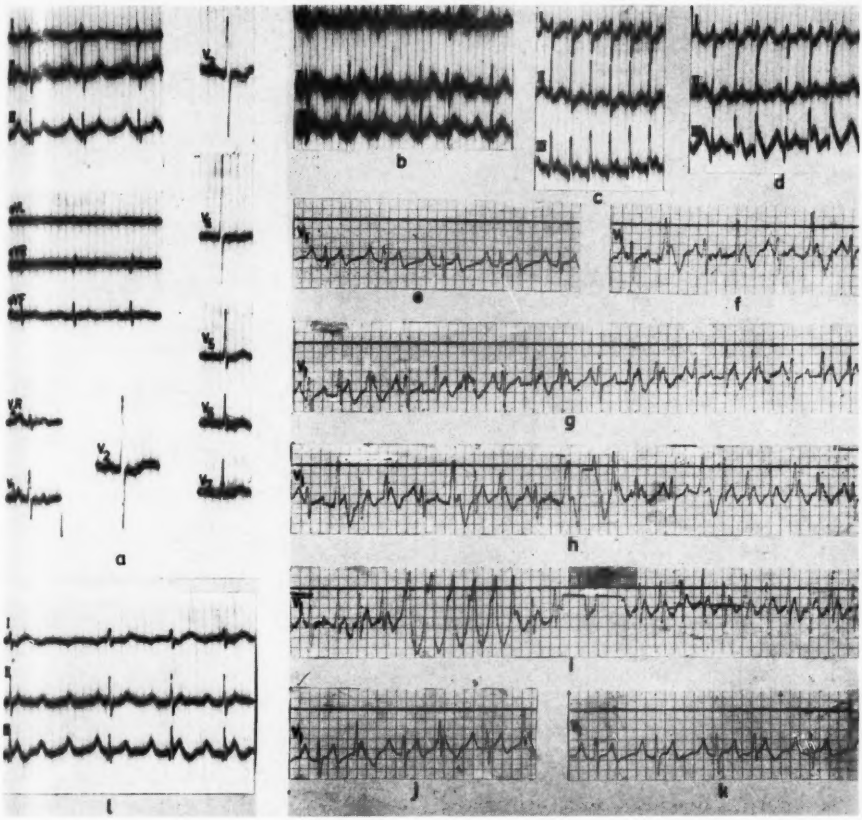

Fig. 2. Case 2, boy A.E., born 1947. Continuous ectopic atrial tachycardia with variable AV block and a tendency to aberrant intraventricular conduction. (*a*) Complete ECG recording at rest, showing habitual mode of conduction (2:1 AV block with prolongation of AV conduction time); (*b*) After slight physical activity (3:2 AV block); (*c*)–(*d*) During orthostatic test: (*c*) immediately after rising up (1:1 AV conduction); (*d*) after 10 min standing (irregular AV conduction with a few aberrant ventricular complexes); (*e*)–(*k*) Exercise tolerance test: (*e*) at rest on bicycle ergometer (2:1 AV conduction); (*f*) after 1 min at 300 kpm/min; (*g*) after 2 min at 300 kpm/min; (*h*) after 6 min at 300 kpm/min; (*i*) after ½ min at 500 kpm/min. (The tendency to facilitation of AV conduction has now resulted in a rapid ventricular rate with aberrant ventricular complexes, probably 1:1 AV conduction with bundle-branch block, possibly ventricular tachycardia.) (*j*)–(*k*) Successive return to ordinary rest picture after end of work test; (*l*) During chronic medication with acetyldigitoxin (0.1 mg daily) and prostigmine (90 mg daily), resulting in increased AV block (recording at rest). Note "normal" AV conduction time following 4:1 block. Time marking = 0.1 sec.

tricles. With increasing ventricular rate, a tendency towards aberration of the ventricular complexes (of RBBB type) was noted. An extreme degree of such aberration appeared during an exercise tolerance test, when a short period of broad and atypical complexes were seen (Fig. 2*i*); on this occasion, a tachycardia of ventricular origin could not be excluded as an alternative explanation. The patient at that time was

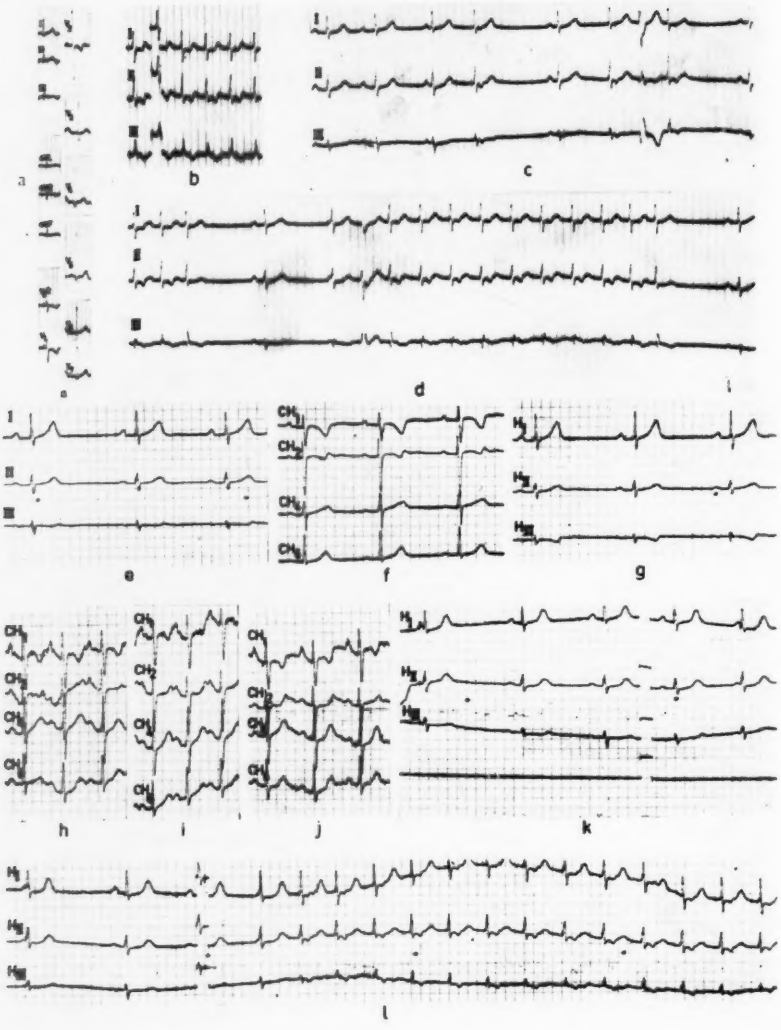

Fig. 3. Case 3, boy K.B., born 1950. Repetitive tachycardia of nodal origin. (*a*) Complete ECG recording; (*b*)–(*d*) Spontaneous variations in cardiac rhythm at rest during the first few years of the observation time: (*b*) and (*c*) Oct. 1956; (*d*) Aug. 1957; (*e*) Spontaneous return to normal sinus rhythm (Jan. 1960); (*f*)–(*l*) Exercise tolerance test (Jan. 1960): (*f*) and (*g*) at rest on bicycle ergometer; (*h*) during work at load of 300 kpm/min, heart frequency about 155 beats/min: (*i*) immediately after work; (*j*) 15 sec after work; (*k*) and (*l*) 2½ min after work. In (k) variations in the P–R time, and in (*l*) a paroxysm of ectopic tachycardia, probably of nodal origin, lasting for about 1 min. Time marking = 0.1 sec.

quite free of symptoms and ready to go on working. Even at other provocation tests he had no complaints, except for some slight dizziness during orthostatic conditions, when a regular tachycardia corresponding to the very high atrial frequency was observed (Fig. 2*c*).

Treatment and subsequent course. Several drugs were attempted but the anomalous type of impulse formation could not be influenced. However, with a combination of digitalis and prostigmine a 2:1 AV block was stabilized, and remained even during orthostatic testing or moderate exercise of an intensity which previously had always provoked tachycardia. This stabilization still persists after 1½ years of medication, and during this period the boy has been completely free of symptoms. A tendency to 4:1 AV block at rest was observed during a period of too high digitalis dosage, and then a "normal" AV conduction time for the transmitted impulse was observed (Fig. 2*a*). The boy was sent home with 0.1 mg of acetyldigitoxin and 90 mg of prostigmine daily. At the latest control in May, 1960, the atrial rate during rest was 150. The AV conduction alternated between 4:1 and 3:1 block, resulting in a ventricular frequency of 40 beats per minute. After 8 min standing, the frequency relation was 160:80 (2:1). An exercise tolerance test was performed with the loads of 200, 400 and 600 kpm/min for 6 min each, and the AV frequency relationships were then 180:90 (2:1), 210:140 (3:2) and 230:230 (1:1), respectively. Even with this very high ventricular frequency the patient was free of symptoms. The tendency to aberration of the ventricular complexes this time was only slight. Because of the marked degree of AV block during rest the digitalis dosage was reduced further.

Case 3. Male patient K.B. born April 11, 1950. According to his mother, he had pertussis in 1953 but otherwise was healthy until the summer of 1955. At that time, he seemed to be tired and had in addition acute attacks of fatigue and irregular heart rhythm with predominantly a high frequency. Otherwise no symptoms. Physical examination (Pediatric Clinic, Karolinska sjukhuset) failed to show anything of pathological significance except cardiac arrhythmia.

ECG. The ECG (Fig. 3) showed an intermittent sino-atrial block and also a varying proportion of ectopic supraventricular, mostly nodal, rhythm. Sometimes only isolated escaped beats were seen. On other occasions, the ECG was dominated by periods of 10–15 beats at a high frequency, separated by periods of 1–3 sinus beats at a normal frequency. During the subsequent years, features of the same kind have been found repeatedly but the proportion of ectopic beats and also the tendency to tachycardia has gradually decreased. Since the beginning of 1959, it has only become manifest in connection with upper respiratory-tract infections. Recent ECG tracings primarily show a sinus rhythm with some slight variations of the P–R interval and of the configuration of the P waves. An exercise tolerance test with a bicycle ergometer has been performed three times. Each time, the cardiac rhythm during work was normal and the working capacity normal according to age and body development. The last time, however, in January 1960, a single paroxysm of tachycardia occurred some minutes after work preceded by a shortening of the P–R time (Fig. 3*a*).

Treatment. Several attempts were made to normalize the heart rhythm by medical treatment. In the autumn of 1956, it was possible with digitalis to obtain a regular sinus rhythm but only with a dosage so high that intoxication resulted (bradycardia, nausea, and vomiting).

The heart volume was checked roentgenologically several times. In June 1958, it was 310 ml, corresponding to a relative heart volume of 370 ml per m^2 body-surface area (BSA); this is a little high. In April 1959, the figures were 270 and 300 respectively, thus suggesting a normalization of the previous slight cardiac enlargement in keeping with the normalization of the rhythm. The change is, however, small.

Case 4. Female patient E.-B.S. born

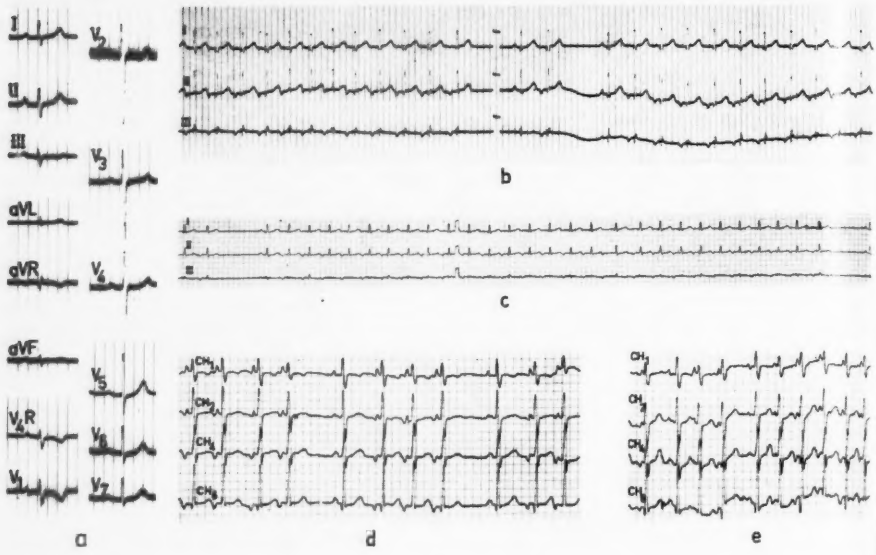

Fig. 4. Case 4, girl E.–B.S., born 1951. Repetitive tachycardia of supraventricular origin. (*a*) Complete ECG recording; (*b*) Standard extremity leads (Oct. 1953); (*c*) Standard extremity leads (May, 1959); (*d*)–(*e*) Exercise tolerance test (May, 1959); (*d*) at rest on bicycle ergometer; average ventricular rate 160 beats/min; (*e*) after 6 min at 300 kpm/min; average ventricular rate 210 beats/min. Time marking = 0.1 sec.

March 15, 1951. In September 1953 she had a mild upper respiratory-tract infection with subfebrile temperature during one day. One week later, at the children's welfare center, a rapid and irregular heart rhythm was detected. No symptoms at this time or ever during the subsequent years. Physical examination never revealed anything remarkable except cardiac arrhythmia.

ECG (*Fig. 4a*). During the whole period of observation, the ECG has been dominated by an ectopic supraventricular (nodal?) tachycardia, frequently interrupted by short pauses followed by single sinus beats. In the first two years, the tachycardia was sometimes interrupted by episodes of bigeminy, with one sinus beat and one ectopic beat in each couple, and occasionally by normal sinus rhythm. During the last three years, the regular finding has been a nodal tachycardia at a frequency of about 150 beats/min, interrupted at intervals of 5–15 sec by a pause and one single sinus beat immediately followed by a new period of nodal tachycardia. No change in the type of arrhythmia occurred during an excercise tolerance test in May 1959. At a load of 300 kpm/min an average ventricular frequency of 210 beats/min was registered without any symptoms.

Treatment. In autumn 1954 an attempt to normalize the heart rhythm with digitalis in a high dosage was made, and sinus rhythm was achieved. When, however, the dosage was lowered to a maintenance level the arrhythmia reappeared. Quinidine treatment following digitalization had no effect on the rhythm.

The heart volume was followed roentgenologically. The relative heart volumeat the age of 3 years 10 months was 240 ml/m² and at 8 years (May 1959) 420 ml/m². Thus, at the last examination a slight cardiac enlargement

TABLE 1. *Case 1.*

Date	Medication	Heart volume, ml Standing	Heart volume, ml Prone	Total Hb, g	Hb conc., g/100 ml	Heart rate, beats/min Rest	300	600	900	1200 kpm/min
1955:										
November	—	1235				64	148	134	170	
December	—	1100	1540	850	16.6	128	128	132	(supine)	
1956:										
June	digitoxin, 0.2 mg/day		1200	1020	14.9	102	94	124	146	164
September	+		1290	940	15.0	56	108	128	156	176
1957:										
January	—		1550	1015	15.4	136	140	140	180	
March	—	1220		1000	16.5	140	168	184	184	184
September	—		1700	934	14.6					
1958:										
April	—			966	17.0	128	144	148	150	168
May	—	1520	1580			128	154	160	160	
July	digitoxin, 0.2 mg/day					62	155	120	150	172
November	+	1090	1340	939	15.8		114	120	150	172
1959:										
May	+	890	1080	885	12.4	76	112	142	172	
December	+	980	940	1020	15.6	76	100	120	146	169

was noted, mainly due to dilatation of the left atrium, which displayed an obvious dorsal bulge towards the esophagus and seemed to be enlarged also to the right. Probably, a slight enlargement of the right atrium was also present. The ventricular part of the heart had a normal appearance.

Discussion

Type of tachycardia

Three of our cases (Nos. 1, 3, and 4) represent the "repetitive" or "repetitive paroxysmal" type of chronic supraventricular tachycardia. The remaining case (No. 2) is an example of 'continuous' atrial tachycardia with variable partial AV block; this case differs from the others by having a normal ventricular rate at rest, but under certain circumstances the ventricular rate may become very high.

Etiology

The etiology of these cases is obscure. In two (Nos. 1 and 4) the case history suggested a correlation in time with a preceding infection but the first beginning of the arrhythmia and tachycardia was in fact not accurately fixed by clinical or ECG examinations. The infections may of course also have been coincidental.

No clinical or laboratory signs of abnormal thyroid function were found.

Symptomatology

In Case 2, of the "continuous" type, subjective symptoms were only noted on those occasions when a high ventricular rate appeared unconnected with muscular effort; palpitations and lassitude were then experienced. Cases 3 and 4, both children, had no subjective symptoms at all from their tachycardia, which was discovered

on routine medical examination. Case 1 had very few if any symptoms from his tachycardia until manhood. Thereafter he sometimes felt tired at rest or on standing still, but improved on muscular exertion and in fact always liked cross-country running. This patient was more closely investigated than the others, and the measurements of blood flows and pressures at rest and during muscular work interestingly illustrate the variability of his subjective symptoms. At rest, left-ventricular stroke volume and arterial pressure were very variable, being low during a run of tachycardia and increasing markedly in the few normal sinus beats. During work, the stroke volume and arterial pressure became more and more stabilized although the ventricular rate did not change much. Apparently, the venous filling improved during work up to the degree needed for the high ventricular rate of the tachycardia.

Clinical course

In Case 3, the tachycardia ended at the age of 8 years after 4 years' duration; in Case 2, the tachycardia still persists at the age of 13 after 8 years' duration; in Case 4, the tachycardia also persists at the age of 9 after 5 years' duration; and in Case 1, the tachycardia seems to have ended definitely ($\frac{1}{2}$ year's observation) at the age of 25 after about 15 years' duration. Therapy, in the form of non-toxic doses of digitalis glucosides, influenced AV conduction but did not abolish the abnormal impulse formation. Quinidine was ineffective except in Case 2 on one occasion. In Cases 2–4, no abnormal clinical signs from the heart apart from the tachycardia have been observed but in Cases 3 and 4 a tendency to roentgenological enlargement was noted. In Case 1, however, clear cardiac enlargement and ECG signs of left-ventricular hypertrophy slowly developed during the duration of the tachycardia. As this patient did not show any signs of valvular lesions, and had a normal arterial blood pressure, the hypertrophy may have been caused by the long-standing tachycardia. The immediate cause of the hypertrophy may then have been the dilatation of the left ventricle which took place during each period of tachycardia with ineffective left-ventricular strokes, as judged from the increasing left-atrial pressure and the low arterial pulse pressure, and which ended in a very large stroke volume in the ensuing normal sinus beat. Digitalis therapy in this patient caused not only increased AV block with slower ventricular rate but also a conspicuous decrease in heart size. Unless the latter effect be ascribed to a positive inotropic influence of digitalis, this reaction to digitalis therapy strengthens the contention that cardiac dilatation and eventual hypertrophy may be a long-term result of chronic atrial tachycardia of the "repetitive" type. No indications of cardiac enlargement were found in the "continuous" type (Case 2).

Summary

Four cases of chronic supraventricular tachycardia are described, three of the "repetitive paroxysmal" type and one of the "continuous" type. The signs of the disturbance started in childhood. Subjective symptoms were scarce.

In the cases of the "repetitive" type, slight cardiac enlargement was noted after

4–5 years' duration in the two youngest patients, while clear left-ventricular hypertrophy was present after 15 years' duration in the remaining patient. It is pointed out that, as signs of valvular lesions, etc. were absent, the tendency to cardiac enlargement may have been the result of the long-standing arrhythmic tachycardia.

Digitalis therapy provoked partial AV conduction block, decreased the ventricular rate, and tended to reduce the cardiac enlargement.

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Intussusception in Children with Acute Vascular Purpura (Schönlein-Henoch Syndrome)

by SIGRID SÖDERLUND

As early as 1808, Willan (18) reported the occurrence of abdominal pain in a case of purpura. Henoch (8) stated in 1874 that abdominal pain may be part of the symptom complex in a certain form of purpura, which he described as a clinical entity. One of the names that has later been given to this form of the disease is acute vascular purpura.

The abdominal pain was considered to be caused by haemorrhages in the intestinal wall. It subsequently became evident that these haemorrhages could give rise to intussusception.

It is true that intussusception is a rare complication of acute vascular purpura. The first case was described in 1893 by Vierhuff (17), and only 33 additional cases have been reported since then (1, 3–5, 7, 9–12, 14, 16, 19). Despite this, the complication is of great clinical interest. It may be difficult to diagnose, and is inevitably fatal unless a prompt diagnosis is made, and adequate treatment—generally surgical—is begun shortly after the onset.

In view of the above-mentioned facts, it seems well motivated to report even single cases of this type.

Two cases of intussusception as a complication of acute vascular purpura occurred at the Department of Paediatric Surgery, Kronprinsessan Lovisas Barnsjukhus, in the spring of 1960. In both cases the diagnosis was initially uncertain, which delayed operation.

Case Reports

Case 1, a boy aged 3 yrs 2 mths, with a history of asthma. Five days before admission, petechial haemorrhages appeared on the scrotum and lower legs, and his feet swelled. On the night before admission, he had acute abdominal pain; he vomited and had one loose, blood-mixed bowel movement.

On admission to the Department of Medicine on the next morning, he was somewhat lethargic and pale. The abdomen was soft, but slightly tender. Petechiae were present on the lower legs and genitals. He had no fever. Blood analyses showed no abnormalities. On this day, he had another blood-mixed defaecation. He vomited repeatedly, and the vomit sometimes contained blood. On the following day he vomited somewhat less, and was able to take fluid by mouth. He had no bowel movement. Two days after admission his general condition was more affected. He vomited repeatedly. Plain films of the abdomen showed marked small-bowel obstruction, and a probable intussusception of the transverse colon. He was transferred to the Department of Surgery, Kronprinsessan Lovisas Barnsjukhus.

His general condition was then greatly affected; he was languid, pale and dehydrated, and tonus was poor. The abdomen was soft but somewhat distended. Slight tenderness was present to the right of the umbilicus. No mass was palpable.

After parenteral administration of fluid, operation was performed 2½ days after the onset of the abdominal symptoms. The abdominal cavity contained blood-stained fluid, and a few patchy, subserous haemorrhages were present on the small intestine. There was ileo-ileocolic intussusception, extending from the hepatic flexure to 40 cm orad to the ileocaecal valve. Reduction was successful, except for the last 20 cm of the small bowel. This part was resected, and the ends exteriorized. The ileostomy was closed 5 days later. Post-operatively, there were numerous recurrences of purpura. On discharge 3 weeks after the first operation, the patient was healthy.

Case 2, a boy aged 8 yrs 4 mths, with several years' history of abdominal trouble, in the form of pain and loose stools. Acute tonsillitis with high fever started 11 days before admission. Penicillin therapy was begun 5 days later. Two days before admission, he began to complain of abdominal pain. He vomited once, and had one passage of dark stools. On the day before admission, he still had pain localized to the lower part of the abdomen. He had one normal defaecation without blood. On the day of admission, petechiae appeared on his elbows and feet.

He was admitted to the Department of Medicine, but was transferred on the same day to the Department of Surgery, Kronprinsessan Lovisas Barnsjukhus. He was then generally affected, pale and dehydrated. Fading petechiae were visible on the elbows and feet. The abdomen was soft, but diffusely tender below the umbilicus, where a mass about 8 by 6 cm was palpable. Rectal examination disclosed normal conditions, and no blood in the ampulla. Urine analyses showed about 10 red cells per visual field. He had no fever. Plain films of the abdomen gave no definite evidence of intestinal obstruction; he was therefore kept under observation for purpura with suspected intestinal bleeding, or an appendix abscess.

On the day after admission, the abdomen was distended. No mass was palpable, but rigidity was present on the left side. Barium meal X-rays showed small-bowel obstruction. At operation 3 days after the onset of abdominal symptoms, blood-stained fluid was found in the abdominal cavity, as well as ileo-ileal intussusception about 100 cm orad to the ileocaecal valve. Since the intussusception was irreducible, about 70 cm of the small bowel was exteriorized, and was resected by diathermy the next day. The ileostomy was closed one week later. The post-operative course was uneventful, and the patient could be discharged in good health 14 days after the first operation.

Discussion

Acute vascular purpura is more common in males than in females. The proportion of males to females given in the literature varies from 2:1 to 3:2 (1, 15). Although the disease may appear at any age, its incidence is highest in children. Sterky & Thilén (15) found, in a series of 224 children, that the onset occurred before 2 years of age in scarcely one-tenth of them, and in half of all the cases between 2 and 5 years. Purpura complicated by intussusception has not, on the other hand, been described in children less than 2 years old, in contrast to intussusception of other origin, which is frequent before this age.

Abdominal complaints often occur in uncomplicated purpura, especially in older children. Thus, in a series of 131 children with this disease, abdominal symptoms were present in one-third of those under 2 years of age, and in three-quarters of those over 2 years (1).

The initial manifestations of purpura are usually localized to the skin or joints. This

applied in my Case 1, i.e., the boy had petechiae and swollen feet for 4 days before the appearance of abdominal symptoms. In rare cases, abdominal complaints may be the first sign of purpura, as in Case 2. In this patient, the petechiae did not appear until unalarming abdominal pain had been present for 2 days.

In uncomplicated purpura, the abdominal symptoms consist of pain, melaena and vomiting. Pain is the commonest symptom. It is often violent, and resembles that of colic. Melaena generally occurs concurrently with the pain. Bleeding may be so profuse that it produces shock. On the other hand, it may be sparse or occult. Vomiting is the most unusual abdominal manifestation. Thus, it occurred in only one-third of a series of 131 cases (1). The vomit may contain blood, as in my Case 1.

Acute vascular purpura may thus be responsible for a symptom complex of abdominal pain, melaena and vomiting, neither skin nor joint symptoms having yet appeared. Numerous cases are, in fact, reported in the literature in which purpura had its onset in the form of abdominal manifestations; laparotomy was performed for suspected intussusception, but disclosed only bleeding in the intestinal wall.

Consequently, when the initial symptoms of uncomplicated purpura are localized in the abdomen, there is a great risk of a faulty diagnosis, with operation as a result. However, this scarcely implies any risk for the patient's life.

The conditions differ when purpura is complicated by intussusception. In this event, the results may be directly fatal if the intussusception is overlooked, or is diagnosed too late. In a few days—or even hours—the disease may lead to intestinal gangrene with a possibly fatal outcome or, in the best case, to recovery after intestinal resection. In such cases, a correct, early diagnosis is of decisive importance for the prognosis. This is confirmed by the literature. Operation was performed in 26 of the 34 cases reported. In 15 of them, the diagnosis was made so late that intestinal resection had to be done. Five of the operated patients died, in every case after resection (1, 11, 12, 14).

The abdominal symptoms of uncomplicated purpura and of intussusception may be highly similar. Consequently, it may be impossible at bedside examination to determine whether or not intussusception is present.

As a rule, no information is provided by palpation of the abdomen. In my Case 1, the intussusceptum could not be palpated, despite the fact that the whole abdomen was consistently soft. Although a mass was palpable on one occasion in Case 2, it was interpreted as an intestinal bleeding caused by purpura, or possibly an appendix abscess. Cases have been reported with a palpable mass, where only an intestinal haemorrhage was found at operation (6, 9). Thus, intussusception was present in only 8 of 18 cases in the literature in which purpura was associated with a palpable abdominal mass (13).

Roentgenologic examination is the most valuable diagnostic aid. In most cases, plain films show whether there is intestinal obstruction. This applied in Case 1. In Case 2, on the contrary, the plain films were not convincing. Intestinal obstruction became evident only after a barium meal examination had been made.

When intussusception is suspected a

barium enema may be valuable from both the diagnostic and therapeutic points of view. This applies if the colon is involved, but not if pure small-bowel obstruction is present. Barium enema examination was not, however, performed in the two cases reported. In Case 1, the intussusceptum was already visible on the plain films. Since intussusception was of such long duration, and the patient's general condition was affected, we did not venture to attempt reduction by barium enema. In Case 2, intussusception was never suspected.

The chief factor responsible for the difficulty of making an early diagnosis when purpura is complicated by intussusception seems to be that the suspicion of intussusception never arises, and that no roentgenologic examination is therefore made. This is illustrated by Case 1, in which the patient was hospitalized for more than two days without intussusception being suspected. The literature contains several cases in which there were no suspicions whatsoever of intussusception, which was detected only at autopsy. In other cases, roentgenologic examination was not made until the patient had marked signs of a serious surgical abdominal condition.

There are no direct indications—consisting either of data in the history or of findings at ordinary clinical examination—that purpura has become complicated by intussusception. Consequently, to avoid intussusception being overlooked, this possibility must be borne in mind in every case of purpura. Even if only mild abdominal symptoms are present, a roentgenologic examination should always be made, in the form of plain roentgenograms and possibly barium enema as well.

Summary

Intussusception is a rare complication of acute vascular purpura. An account is given of two personal cases. Intestinal resection was necessary in both of them, since operation was delayed by the diagnosis being uncertain. It is pointed out that the abdominal symptoms in uncomplicated purpura and in intussusception may be highly similar. Consequently, it is difficult to decide whether purpura has been complicated by intussusception. An incorrect diagnosis is fatal in such cases. It is recommended, in order to avoid intussusception being overlooked, that roentgenologic examination—in the form of plain films and possibly barium enema as well—be made in every case of purpura in which abdominal symptoms are present.

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Studies of the Circulatory Adaptation Immediately after Birth

by GÖRAN WALLGREN, PETTER KARLBERG and JOHN LIND

The most urgent problem the newborn infant has to face is the initiation of breathing and the subsequent respiratory and hemodynamic adaptation to extrauterine life. The literature on this subject during the last years has been abundant; for recent general reviews see Cook *et al.* (3), Karlberg (14), James (12), Stern & Lind (18). Nevertheless knowledge regarding circulatory adaptive changes in connection with the initiation of breathing is limited and for the most part has been extrapolated from studies of the status of the circulation before, as well as after, delivery (6, 14), and from studies in animals (6).

Respiratory studies have demonstrated that the transformation of the fetal lungs to an organ which functions adequately for respiratory gas exchange proceeds very rapidly indeed; it is principally achieved during the first few breaths (8, 14). For this reason it is necessary to register and interpret the circulatory dynamics during this transformation and to correlate them with studies of the respiratory adaptation.

The present communication reports observations on the blood pressure recorded in the umbilical vessels in the newborn infant immediately post partum and during the first minutes of extrauterine life and the influence on arterial pressure of intrathoracic pressure variations.

Material

Ten fullterm infants with spontaneous vertex delivery from healthy mothers were studied. The pregnancies were uneventful and all of the deliveries were considered normal, except one (Case 7), when it was necessary to clamp and cut the cord before delivery of the body. Maternal anesthesia consisted of nitrous oxide which was given to the mother intermittently during the later part of labor and chloroform for a short period during delivery. Following delivery the infant and the intact umbilical cord were placed at a level 5–10 cm below the mother's perineum. Resuscitation was not required in any case and all infants began to breath within 20 seconds of birth. All had a normal course during the neonatal period.

Methods and Procedure

Blood pressure in the umbilical vessels were recorded through a needle with an internal diameter of 1 mm, attached to the end of a no 6 Cournand heart catheter, connected to a strain gauge manometer (Elema). The system was filled with sterile isotonic saline and was flushed at regular intervals to insure unhampered pressure recording: One of the umbilical arteries was punctured 5–10 cm from the umbilicus with the needle pointing towards the infant. The vein was punctured approximately 20 cm from the vulva, the needle directed towards the placenta. Intraesophageal pressure was recorded through a saline-filled polyethylene catheter (13), with an internal

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diameter of 1 mm and with perforations in the sides and end of the tip. The catheter was introduced through the mouth immediately after the delivery and placed with the tip approximately at the junction of the middle and the upper third of esophagus. The strain gauges were placed 3 cm above the table to avoid hydrostatic effects. The signals from the three manometers were simultaneous recorded on a multi-channel recorder (Elema mingograph).

The recordings were started within 5 to 35 seconds after delivery and were continued for 1–2 minutes, in general until the umbilical arterial pulsations ceased. Care was taken to handle the cord as gently as possible during the whole procedure and pulsations in the cord were not observed to change by the introduction of the needle. In six of the cases recordings were started before or at the onset of respiration. In the remaining four cases the infants breathed 2 or 3 times before tracings were obtained. For technical reasons venous pressure was recorded in only 6 infants. The pressure recordings from the umbilical artery has been considered to be representative of the systemic arterial pressure of newborn infants (21) and intraesophageal pressure changes are considered representative of intrathoracic pressure changes (13).

Results

"Basal" pressure in the umbilical artery. The "basal" arterial pressures and the pulse rate in such periods are listed in Table 1 and the time in relation to the onset of respiration for each of the ten infants. As defined "basal" pressures were those recorded between respiratory movements or during shallow respiration because marked pressure variations in blood pressure occurred synchronously with forceful respiratory movements. Initial blood pressure ranged from 40/21 to 95/73 mm Hg. There was a relatively wide range in the pressures recorded immediately before and after the first breath but no systematic change was observed. After the infant had breathed for 10–20 seconds the blood pressure during the period of recording was constant within a range of 15 mm Hg. Twenty to thirty seconds after the onset of respiration the mean "basal" blood pressure was 69/45 mm Hg. There was marked variation in pulse rate which did not show any systematic change.

Influence of the intrathoracic pressure variations on the pressure in the umbilical arteries. The most striking feature in the arterial pressure curves was the great variation in both systolic blood pressure and pulse pressure which occurred synchronously with pressure variations within the thorax (Fig. 1). This influence was most obvious when the greatest intrathoracic pressure variations occurred but it was even apparent during less forceful respiratory movements. Forced expiration (positive intrathoracic pressure) resulted in increased systolic, diastolic and pulse pressures; increased negative intrathoracic pressure resulted in a fall in these pressures. The most marked variation in the arterial pressure and the shape of the pulse wave occurred synchronously with abrupt rises or falls in intrathoracic pressure when the change coincided with a pulse stroke (Fig. 1–2). At these times pulse amplitude more than doubled during a forced expiration and almost disappeared during forced inspiration.

Pressure in the umbilical vein. The umbilical venous pressure about 10 seconds after the first breath ranged 15–50 mm Hg. At around 100 seconds it had fallen to 10–20 mm Hg.

TABLE 1. *Pressure in umbilical artery and pulse rate in relation to time of the first breath.*

Case nr	Time in sec. relative to 1st breath	−20	−10	0	10	20	30	40	50	60	70	80	90
1	B.P.					66/55		55/43	60/46		70/50		
	Pulse					120		150	175		150		
2	B.P.			95/73		56/38							
	Pulse			120		150							
3	B.P.			70/40	69/47		74/49		84/55				
	Pulse			165	150		150		159				
4	B.P.		54/39		69/45		72/48	66/42	66/39		66/45		
	Pulse		150		150		145	140	110		130		
5	B.P.		72/42		45/35		66/35						
	Pulse		144		86		110						
6	B.P.				45/30		53/30	51/27					
	Pulse				110		110	115					
7	B.P.					40/21	42/21	42/18					
	Pulse					165	160	170					
8	B.P.		75/42		71/35	83/45		73/32	83/46	81/50	80/48	86/57	82/53
	Pulse		80		80	120		72	140	142	140	160	158
9	B.P.			93/66		87/46	84/48	84/48	86/55				
	Pulse			72		100	86	110	110				
10	B.P.				75/57	73/57	71/35						
	Pulse				170	140	100						

Discussion

Pressure measurements in the umbilical vessels during the immediate neonatal period have been performed by several investigators. Hasselhorst (9) reported an average systolic pressure of 75 mm Hg in the umbilical artery and a value of 26 mm in the umbilical vein. He also recorded pressures when the baby was still in the uterine cavity after incision in the uterus and found no systematic difference in the arterial and venous pressures before or after delivery. Woodbury *et al.* (21) reported an average pressure in the umbilical artery of 80/46 mm Hg in a series of 24 normal deliveries. These authors observed an increase in systolic and diastolic pressures during crying, the average rise being 27 mm Hg. Nyberg & Westin (17) found similar values in the umbilical artery in the time range of 6–80 seconds after birth. They, too, noted great variations in the pressure levels synchronous with respiratory movements. In the present investigation the average value calculated from the "basal" pressure in the umbilical artery 20–30 seconds after the initiation of breathing was 69/45 mm Hg,

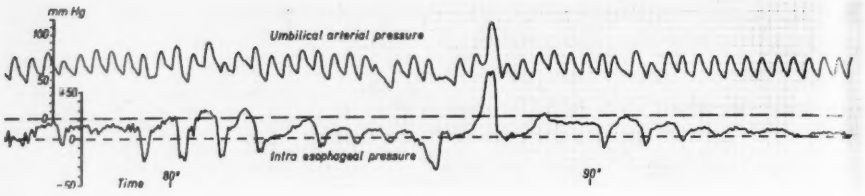

Fig. 1.

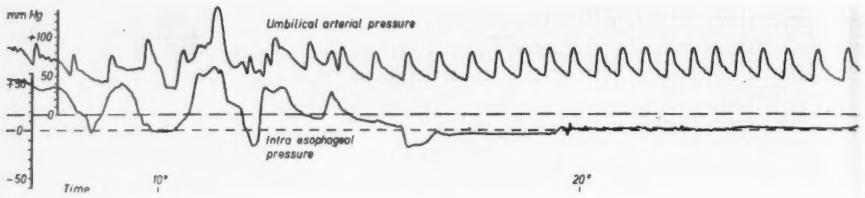

Fig. 2.

Fig. 1 and 2. Pressure tracings in the umbilical artery and esophagus in two newborn infants.

and is thus in agreement with earlier reports. Case 7 is excluded from this calculation because of the abnormal course of the delivery.

The stable level of the basal systemic pressure in the child before and after delivery, as well as before and after the first breath speaks in favor of an effective regulatory mechanism, which secures circulatory homeostasis. At birth sudden changes in environmental temperature and pressure and the distribution of blood into the rapidly increasing pulmonary circulation greatly alters circulatory demands. These circumstances would result in a hypovolemic state similar to that of circulatory shock, if they were not counterbalanced either by increase in the peripheral vascular tonus or by transfusion of blood to the child. The former possibility seems less likely in view of the findings of Young & Holland (22), who observed that there is no rebound blood pressure increase after tilting the body feet down during the very first days of life but there is a marked increase in the pulse rate. It is then more probable that the discrepancy between blood volume and vascular capacity in the newborn infant is corrected by the transfusion of blood from the placenta, which apparently occurs during delivery and immediately postnatally. Hörman *et al.* (11) calculated the net shift of blood from the placenta to the child after delivery and found that an average of 70 ml was transfused to the child, and that around 75 % of this volume was transfused during the first minute. Whipple *et al.* (20) have shown that it occurs within 15 seconds of delivery. A shift of blood of this magnitude to the newborn infant who, at full term, has a total blood volume of approximately 300–350 ml, may be sufficient to correct the disproportion between the amount of available blood and the changing capacity of the vascular beds. In this connection it deserves mentioning that the average addition of blood from the

placenta to the neonate constitutes approximately 20% of the total blood volume of the child, a figure which is almost exactly the same as the lung blood volume in relation to total blood volume in the healthy adult (15). Since studies in newborn animals (4) have shown that a marked decrease in the pulmonary resistance is caused by the inflation of the lungs with air and studies in newborn infants (14) have shown that considerable aeration of the lungs occurs during the first few breaths there is reason to assume that a marked increase of the blood volume in the lungs will take place before flow in the umbilical vein has ceased.

The findings in Case 7 may be explained by the deprivation of this transfusion of blood from the placenta due to the clamping of the cord before the delivery of the body. Lind & Wegelius (16) observed a dramatic reduction in the heart size during inspiration of the first breath when the cord was clamped before the first breath. This was not observed when the cord was patent from which they concluded that there is a shift of blood from the placenta to the child during the initial inspiration which is important in maintaining an adequate stroke volume and, thus, circulatory homeostasis.

Although the "basal" systemic pressure is kept constant during the immediate postnatal period, there are great changes in the arterial pressure curve with individual breaths. The intimate relationship between systemic blood pressure variations indicates that the variation in blood pressure is a secondary phenomenon to the respiratory movements.

The effect of intrathoracic pressure variations upon the circulation has been thoroughly studied in adults (1, 2, 10). Although there is a marked respiratory influence upon the circulation, there is little effect on systemic arterial pressure (19).

Changes in the pulse pressure are caused by alterations of stroke volume and/or peripheral resistance. In newborn infants with the ductus arteriosus patent a change of the pulmonary resistance will directly influence the systemic resistance. Positive intrathoracic pressure increases the transmural pressure in the lung vessels resulting in increase of pulmonary vascular resistance. The left to right shunt through the ductus is then decreased, stopped or even reversed. Thus systemic blood pressure associated with inspiration rises. On the other hand, with negative intrathoracic pressure, associated with inspiration, the vascular resistance in the lungs decreases, promoting an increase of the left to right shunt through the ductus.

Since there is no reason to believe that the effects of intrathoracic pressure upon venous return to the left heart are different in infants than adults, it seems clear that changes in aorto-pulmonary shunting are the principle explanation of the pronounced influence of intrathoracic pressure on systemic blood pressure. Such an interaction has been shown in adults with persisting patent ductus arteriosus where the shunt through the ductus has been modified during operation (7).

Beat to beat analysis of the shape of the peripheral pulse wave and its change with intrathoracic pressure variations are in progress.

Summary

Simultaneous pressure measurements in the esophagus and an umbilical artery

were performed in ten full-term infants following spontaneous vertex delivery. The recordings were started within 5–35 seconds and continued for 1–2 minutes. In six of the cases recordings were started before or at the onset of respiration. The average values were found to be 69/45 mm Hg. A stable "basal" systemic pressure was found before and after the first breath, in spite of the sudden change in environmental conditions at birth and the suddenly increasing pulmonary circulation. Several observations are presented which indicate that the placental transfusion may be balanced between the amount of available blood and the increasing capacity of the vascular bed in the newborn infant, thus securing circulatory homeostasis. A striking feature was the direct relationship between the intrathoracic pressure and the arterial pressure. An increase in both systolic, diastolic and pulse pressures occurred during increased positive pressure in the thorax during expiration and a decrease during the inspiratory negative pressure. The intimate correlation between the intrathoracic pressure and the pulse amplitude is primarily attributed to changes in the aorto-pulmonary shunting through the ductus arteriosus.

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Respiratory Studies in Children

VIII. Respiratory Adaptation during Exercise Tolerance Test with Special Reference to Mechanical Properties of the Lungs in Asthmatic and Healthy Children[1]

by INGA ENGSTRÖM, PETTER KARLBERG, SVEN KRÆPELIEN and GISELA WENGLER

The ventilatory capacity of children with bronchial asthma may undergo changes, manifested in lowered maximal breathing capacity and forced expiratory volume even during periods when the children are free of symptoms (3, 5). When studying the ventilatory capacity by these methods, the ventilation is evaluated during short periods of 15 seconds and 1 second, respectively, of maximal forced breathing. Since ventilatory efforts of this degree far exceed those required in response to any functional demand, even maximal exertion, the question arises whether there are disturbances of lung function in these children during periods of increased ventilation imposed by physical exertion and whether, in fact, these children have an impaired exercise tolerance. Although several ventilatory studies of adult asthmatic patients during exercise have been reported (7, 11, 12, 17), similar studies are not reported in asthmatic children. Tests made on adult patients with bronchial asthma may not be directly compared with results in children since the hyperinflation of the lungs encountered in asthmatic children during symptom-free periods (16) may be reversible (14, 15) and, therefore, of functional origin to a large extent, whereas many adults have irreversible organic lesions (emphysema).

The purpose of this study was to investigate the lung function under conditions of functionally increased ventilation. Exercise tolerance tests were performed on a group of children with bronchial asthma and for comparison on a group of healthy children. Since determination of working capacity provides only an indirect measure of the adaptability of ventilation and includes many other functional factors, especially circulatory, it was believed that more definite tests of lung function should be performed. Thus, during the exercise tolerance test changes in respiratory rate, tidal volume, lung compliance and pulmonary flow resistance were recorded.

[1] Aided by a grant from the Swedish National Association against Heart and Chest Diseases.

Material

Exercise tolerance tests were performed on thirty-eight children with bronchial asthma, 20 boys and 18 girls, 7–15 years of age. The children were selected from patients attending the Allergy Out-patient Departments and Allergy Departments at the Pediatric Clinic, Karolinska Sjukhuset and the Sachs Children's Hospital. The severity of the illness was classified clinically according to the annual frequency of asthma attacks in the same way as previously described (3, 5, 16). Thirty-four of the subjects were examined during symptom-free periods (at least three days of freedom from symptoms without symptomatic treatment prior to examination). Four children were in a clinically labile state and were therefore under symptomatic treatment at the time of examination. Twenty-six of the subjects were classified as Group I with less than five attacks per year, and four were classified as Group II with between five and ten attacks per year. The remaining eight children (including the four clinically labile) were in Group III with more than ten attacks per year or with prolonged status asthmaticus. The mechanics of breathing during exercise were studied on ten of these children, three in Group I, one in Group II and six in Group III, the latter including the four clinically labile. Comparative studies were made on a group of 38 healthy children, 15 boys and 23 girls in the same age groups. They were schoolchildren without evidence of pulmonary or cardiac disease and were selected to provide a fairly even age distribution. The condition of physical training was not a factor in the selection. Eleven of these healthy children were chosen at random for determination of the mechanics of breathing during exercise.

Method

The exercise tolerance test was performed on a bicycle ergometer with increase of pulse rate as indicator of the intensity of effort ad modum Karolinska Sjukhuset (21, 22). The subjects were tested without pause at two successive loads, 6 minutes at each load. The loads were chosen as proposed by Bengtsson (2). The initial load was predicted to result in a pulse rate of around 140 per minute, the second around 170 per minute. Pulse was measured every second minute during the test. As a measurement of exercise tolerance the working capacity in kilopondmeter per minute (kpm/min) at a pulse rate of 170 was used. This value is calculated by interpolation or extrapolation from the assumed rectilinear relationship between the loads during the two periods and the pulse rates at the end of each period.

Respiratory rate was counted at rest before the exercise and during the last minute of the two load periods, and at the same time the expired air was collected in a bag and the volume measured in a dry gas meter.

The mechanical properties of the lungs were studied first at rest, then during the last minute of each period of load, and finally at rest within 6 minutes after exercise. The respiratory volume was determined by letting the child breath into an airtight box of roughly 1500 liters volume. The resulting pressure variations in the box were picked up by an electromanometer and registered on a direct writing recorder (Elema mingograph). A record of air flow was obtained by electronic derivation. The volumes were corrected to BTPS. The changes of intraesophageal pressure were used as an index of intrapleural pressure variations. A latex balloon affixed to polyethylene tubing was passed into the esophagus through the nose and connected to a second electromanometer, which picked up the intraesophageal pressure variations recorded on a third channel of the direct writing recorder. It was thus possible to record simultaneously tidal volume, air flow and intraesophageal pressure variations. From these data respiratory rate, tidal volume, lung compliance ($\Delta V/\Delta P$) and pulmonary flow resistance ($\Delta P/\Delta V/t$) were calculated. The apparatus and method are described in detail elsewhere (13).

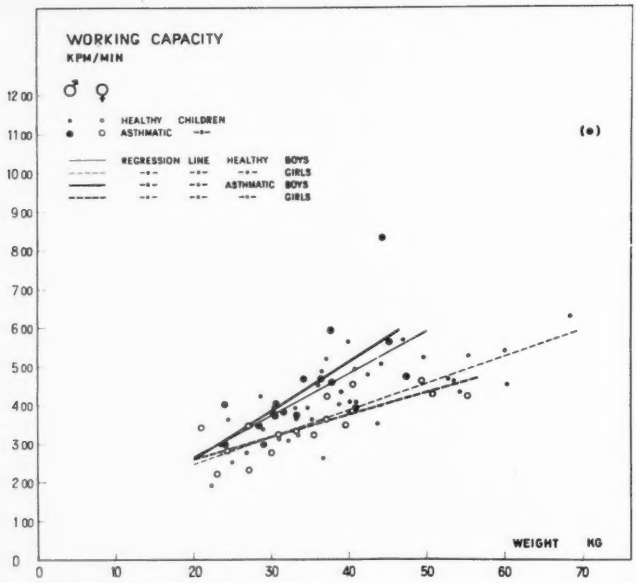

Fig. 1. The working capacity (y) at a pulse rate of 170/min in relation to body weight (x). The calculated regression lines are drawn. Regression equations: healthy boys $y = 10.84\,x + 45$; healthy girls $y = 6.89\,x + 109$; asthmatic boys $y = 12.64\,x + 4$; asthmatic girls $y = 5.72\,x + 145$.

Results

Working Capacity

Both the healthy children and the asthmatic children examined during symptom-free periods were able to complete the exercise tolerance test. Three of the asthmatic children, however, had ronchi immediately after the exercise. As in earlier studies on children (2), the working capacity calculated at a pulse rate of 170 per minute showed good correlation with body weight (Fig. 1). Regression calculations according to Snedecor (20) were made both for the healthy and the symptom-free asthmatic children with boys and girls separated. The regression lines obtained are drawn in the diagram and show higher working capacity in boys than in girls in relation to body weight in both groups. These differences when tested by analysis of covariance were statistically significant ($P < 0.001$). The slight differences found between healthy and asthmatic children of the same sexes are not statistically significant ($P > 0.1$). Three of the four clinically labile children were unable to complete the second load test period despite an expected pulse reaction during the first load (one of them developed ronchi as result of exercise) and could consequently not perform an exercise corresponding to a working capacity predicted from the body weight. The fourth child in a state of clinical lability could complete the test only when very low loads in relation to his body weight were used. All four of these children must be considered to have a low exercise tolerance.

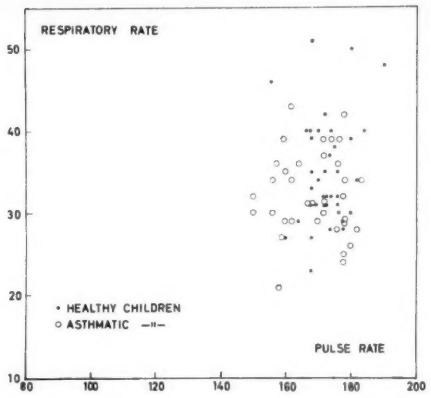

Fig. 2. Respiratory rate in relation to pulse rate at the end of the second work load.

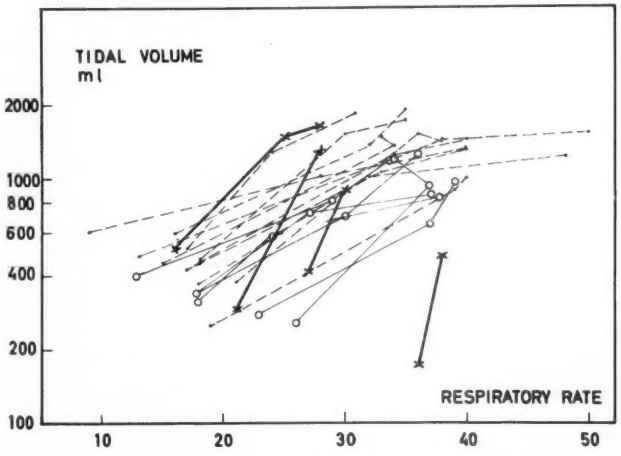

Fig. 3. Tidal volume at rest, and at the end of the first and second work loads in relation to the corresponding respiratory rate. · – – – – · healthy child, ○——○ symptom-free asthmatic child, ×——× asthmatic child in a clinically labile state.

Ventilation

The relation between respiratory rate and pulse rate at the second load is illustrated in Fig. 2. The scatter is considerable within each group and no difference is noticeable between healthy and asthmatic children. Nor was there any noticeable difference between the two groups regarding the increase of minute volume per kpm/min. In the healthy and asthmatic children whose mechanics of breathing were measured, the relation between the percentage increase in tidal volume and the increase in respiratory rate

TABLE 1. *Mechanical properties of the lungs in healthy children during rest, during exercise and during recovery within 6 minutes after exercise.*

Case	Age, years	Working cap./170 kpm/min	Respiratory rate			Tidal volume, ml			Lung compliance, ml/cm H_2O			Pulmonary flow resistance, cm H_2O/lit/sec		
			Rest	Load II	Rest	Rest	Load II	Rest	Rest	Load II	Rest	Rest	Load II	Rest
LE	11 9/12	365	19	40	21	248	1008	350	74	85	88	4.4	5.3	4.8
CM	12 8/12	375	18	40	18	450	1445	385	74	81	85	4.8	7.1	5.8
AÅ	14 2/12	430	13	50	12	484	1553	660	104	89	103	8.5	4.8	4.3
MK	13 3/12	535	16	35	18	594	1920	660	185	156	123	5.1	4.3	4.4
IH	13 8/12	450	17	31	21	515	1850	670	111	146	122	3.8	3.9	3.2
EK	10 8/12	450	17	40	15	425	1340	402	85	94	108	6.4	5.6	2.2
AMH	11 6/12	460	18	35	23	464	1730	485	120	197	184	4.1	3.5	1.6
JS	15 3/12	430	21	38	21	376	1410	435	85	93	121	5.3	5.3	3.4
HS	12 2/12	405	15	33	18	450	1490	438	126	154	134	6.3	6.7	4.5
SÅ	11 9/12	390	18	48	18	370	1240	407	85	70	68	4.9	8.8	4.0
KJ	11 2/12	485	9	40	15	608	1335	790	79	87	98	10.8	7.5	4.4

for each load was similar with the exception of the clinically labile children. In these four children tidal volume increased disproportionately more than respiratory rate (Fig. 3).

Mechanical Properties of the Lungs

The observed values are listed in Table 1 and 2. In eight of the healthy children lung compliance was essentially constant during exercise with differences ranging from -16 to $+15\,\%$ between the values at rest and during the second load. In the remaining three cases the lung compliance was increased with values 22, 32 and 64 % higher during exercise. The mean percentage change of all the healthy children was $+13.5\,\% \pm 6.5$ (t-test $0.1 > P > 0.05$), i.e. as a group there may be a tendency to increase. The pulmonary flow resistance of the healthy children, on the other hand, showed no systematic variation during exercise, the mean percentage change being $+3.7\,\% \pm 10.7$, but a significant decrease occurred after exercise in relation to the initial value at rest, the mean percentage change being $-28.9\,\% \pm 8.3$ ($P < 0.01$).

Among the ten asthmatic children the lung compliance increased in 7 cases more than 27 % and was fairly constant in the remaining three, the mean percentage change amounting to $+82.0\,\% \pm 35.5$ ($P < 0.05$). In three of the cases the increase was considerable, 130, 181, 350 %. Two of them belonged to the clinically labile group and failed to complete the test, whereas one completed the test at normal load. Pulmonary flow resistance in the asthmatic children showed a general decrease during and after exercise in all cases but one. In the one exception the resistance rose markedly after exercise and the child had ronchi and expiratory dyspnoea. The mean percentage decrease during exercise among the nine cases behaving uniformly showed a statistically significant decrease, $-15.2\,\% \pm 5.3$ ($P < 0.02$). At rest after completion of exercise the pulmonary flow resistance is even more

TABLE 2. *Mechanical properties of the lungs in asthmatic children during rest, during exercise and during recovery within 6 minutes after exercise.*

Case	Age, years	Working cap./170 kpm/min	Respiratory rate			Tital volume, ml			Lung compliance, ml/cm H_2O			Pulmonary flow resistance, cm H_2O/lit/sec			Clinical condition	Group[a]
			Rest	Load II	Rest	Rest	Load II	Rest	Rest	Load II	Rest	Rest	Load II	Rest		
GS	12 3/4	295	18	37	18	343	847	363	78	183	98	6.2	4.3	5.2	Symptom-free	I
BA	8 11/12	295	23	39	23	278	945	357	99	127	176	6.0	6.6	4.5	Symptom-free	I
AW	11 9/12	330	26	34	23	255	1190	324	59	77	111	5.2	4.9	3.5	Symptom-free	I
MN	9 10/12	275	13	34	18	407	1220	418	141	133	98	7.8	6.4	3.5	Symptom-free	III
TL	10 11/12	455	18	36	36	336	1270	1473	121	111	106	5.5	4.4	5.0	Symptom-free	II
BA	8 8/12	345	18	38	22	317	835	467	70	124	75	11.1	12.0	26.1	Symptom-free before, ronchi & dyspnoea after	III
GA	8 10/12		36	30[b]	48	160	442[b]	292	101	454[b]	316	6.3	5.6[b]	4.4	Clinically labile, ronchi after	III
EA	11 3/12		27	30[b]	20	423	896[b]	485	72	79[b]	67	7.5	7.3[b]	5.6	Clinically labile, ronchi	III
IB	11		21	28[b]	—	286	1330[b]	—	84	236[b]	—	9.0	8.0[b]	—	Clinically labile	III
LF	14 3/12	300	16	28	16	523	1650	791	173	219	201	6.3	3.3	5.5	Clinically labile	III

[a] Grouping according to annual frequency of attacks (see text).
[b] Values from the end of the first load period.

decreased in relation to the initial value at rest, the percentage amounting to $-26.0\,\%$ ± 5.0 ($P < 0.01$) calculated on eight cases (in one child it was not possible to obtain a record after exercise).

Discussion

Since the test was completed by all asthmatic children examined during symptom-free periods, the working capacity at a pulse rate of 170 per minute could be calculated ad modum Karolinska Sjukhuset. Even if the pulse rate during maximal exertion diminishes with rising age (1, 19), it is justifiable to use this method of calculating working capacity, when a control group of healthy children of the same age distribution are simultaneously investigated.

Previously reported studies from this laboratory have shown that the ventilation of children with bronchial asthma is often disturbed even during asymptomatic periods (16), which would lead one to expect an impaired tolerance in these children. This same conclusion is suggested by their medical histories which often reveal a greater inclination to dyspnoea and less endurance than in children of the same age even during clinically free periods. Another reason for expecting an impaired exercise tolerance is that their physical conditioning may be inferior, since in general they do not participate actively in gymnastics or sports. Yet the tests show no significant difference in working capacity between healthy and these asymptomatic asthmatic children in relation to sex and body size. This means that, if ventilatory disturbance is present, it is not serious enough to prevent an adequate increase of ventilation during the periods of increased exertion induced under laboratory conditions. Since there was no difference in tidal volume or respiratory rate in the two groups of children during exercise, there is no evidence to suggest that the asthmatic children use a different compensative mechanism for maintaining adequate ventilation during this period.

In the clinically labile subjects decreased exercise tolerance was clearly shown as well as an impaired ability to increase respiratory rate, with increase of minute volume produced chiefly through an increase of tidal volume.

The reported ventilatory studies during exercise that have been performed in adult asthmatic patients (7, 11, 12) have also shown an impaired ventilation among the severe cases. The limiting factor, however, has been the inability to increase tidal and minute volume, probably because of organic changes of the lungs, emphysema.

Reports in the literature about the mechanics of breathing are contradictory and are limited to studies in adults. McIlroy *et al.* (18) found a substantial increase in compliance and a decrease in non-elastic resistance in healthy persons during exercise, while Granath *et al.* (10) found no change. Our results in healthy children have not been consistent as regards change in lung compliance during exercise: in three cases a probably significant increase occurred but there were unsignificant changes in the remainder. No systematic variation in pulmonary flow resistance was observed during exercise but a significant decrease after completion of exercise. Since an increased rate of breathing would in itself affect the recording of the mechanics of breathing, tests

were made on eight children during periods of different respiratory rates regulated by a metronome (20, 30 and 40 breaths a minute) with only slight increase in tidal volume. No systematic change was found, however, the mean percentage change between the values at respiratory rates of 20 and 40 breaths per minute being for lung compliance $-2.1\% \pm 11.3$ and for pulmonary flow resistance $-5.0\% \pm 8.9$. Thus, an increased frequency of breathing alone does not appear to be responsible for the changes recorded during exercise.

A comparison of the mechanics of breathing of healthy and asthmatic children during exercise shows that the direction of change in the two groups is similar, although the changes are somewhat more pronounced in the asthmatic children than in the healthy children. These changes are the reverse of those observed during a provoked asthmatic attack; there one observes an increased pulmonary flow resistance and a decreased compliance (4, 6). The child with manifest expiratory dyspnoea following exercise was the only one who had an increase of pulmonary flow resistance.

The significant decrease in pulmonary flow resistance in the asthmatics during and after exercise must be looked upon as an effect of bronchodilatation. This may be due to the increased catecholamine incretion found during exercise (8).

Compliance has been observed to increase after a series of deep breaths, possibly because a larger number of alveoli are ventilated (9). The same mechanism may conceivably accomplish the increase of lung compliance in conjunction with the hyperventilation produced by exercise, although it is questionable whether such a large increase as we have found in some of the asthmatic children could be solely caused by this mechanism. The changed circulatory conditions during exercise may also affect the mechanics of breathing, especially in asthmatics with their functional lability. It is equally unknown how long the increased compliance and reduced pulmonary flow resistance persists following exercise. These questions require further study.

Summary

An exercise tolerance test was performed on 38 asthmatic children and on 38 healthy children. The working capacity in relation to body weight of asthmatic children examined during symptom-free periods was equal to that of healthy children, but was inferior in asthmatic children examined in a clinically labile state.

The increases of respiratory rate, tidal volume and minute volume during work were similar in healthy children and asthmatic children except in the clinically labile subjects who had impaired ability to increase respiratory rate.

The mechanics of breathing were studied in 11 healthy children and 10 asthmatic children during exercise. In healthy children the lung compliance showed a tendency to increase and the pulmonary flow resistance no systematic variation during exercise but a significant decrease after exercise. The asthmatic children as a group showed a significant increase in lung compliance during exercise and a significant decrease in pulmonary flow resistance during and after exercise. The possible mechanisms are discussed.

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Roentgenologic Examination of Rectum in Ulcerative Colitis

by ULF RUDHE

In the roentgenologic examination of ulcerative colitis, the main interest has been focused on the lesions localized to the colon. On the other hand, only brief mention has generally been made in current literature of the roentgenologic aspects of the inflammatory process in the rectum. In the present investigation, the rectum and the perirectal tissue have been studied from the roentgen-diagnostic point of view, in the series of ulcerative colitis of which an account is given elsewhere in this issue by Ehrenpreis *et al.* (1). The object was to correlate the changes demonstrated at roentgenologic examination with those observed at proctoscopy, at operation and in excised specimens. In addition, an attempt has been made to analyze the value of roentgenologic studies of the rectum, regarding both the choice of operative method, and evaluation of the effect on the rectum when, after colectomy, it has been anastomozed to the ileum, or isolated.

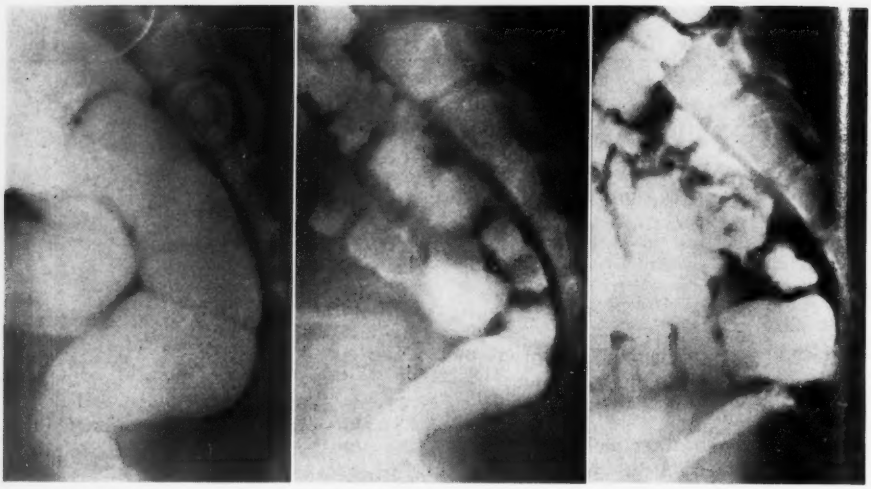
Case Material and Methods

A roentgenologic examination with barium enema was made one or several times in 23 individuals, aged 4–18 years at the time of their first admission. The case material is the same as that in the report of Ehrenpreis *et al.* (1), to which reference is made for the clinical data and observations at roentgenologic examination of the colon and ileum.

The rectum was depicted routinely in the frontal and true lateral projections; in about half the cases oblique projections were used as well. In five cases, special exposures of the rectum were made after evacuation of the contrast medium. In six cases, complementary studies were made of the rectum after inflation. Post-operative roentgenologic examination was performed in all but three cases.

The average focus-film distance in the examinations was 85 cm. The enema was injected from a level of 60–75 cm above that of the examining table. The exposure time ranged from 0.3–0.8 sec at 350 mA and 100 kV. The dose to the gonads was not determined but, on the basis of the studies presented by Forrester & Soule 1960 (2), it can be estimated at 0.7 r on exposure in the lateral projection in girls. A considerably lower value is recorded in boys.

The normal variations in shape and size of the rectum and retrorectal space at the ages in question were analyzed on the basis of roentgenologic examination of 40 subjects, who had no clinical indications of any inflammatory process of the rectum. The borderline between rectum and sigmoid was fixed at the level of the 3rd sacral vertebra. As in adults, the rectum runs closely along the anterior surface of the sacrum and, when the rectum is distended, both its ventral and lateral portions have a distinctly convex margin. Distension of the urinary bladder



a *b* *c*

Fig. 1. Lateral view of rectum and sacrum in a 9-year-old child with no rectal disease. In (*a*), in which the rectum is distended, the retrorectal tissue on the level of the 4th sacral vertebra measures 3 mm; in (*b*), in which there is less distension, 4 mm; and in (*c*), after evacuation of enema, 5 mm. The rectal folds have the normal appearance.

produces deformation of the rectum, particularly of its ventral part. Of the three folds normally present in the rectum, only the middle one (Kohlrausch's fold) can, almost consistently, be identified at roentgenologic examination.

The space between rectum and sacrum—which is delimited by the retrorectal and presacral fascias—is of minimum width on the level of the 4th sacral vertebra. Under normal conditions and in the age group in question, the thickness of this retrorectal space on the level of the aforementioned vertebra is 3–7 mm on the roentgenogram. After evacuation (10 children with no rectal disease), the distance between the rectal lumen and the sacrum increases by 2–5 mm, depending on the degree of contraction of the rectum (Fig. 1). The wall of the rectum is 1–2 mm in thickness, and in the contracted state 3–4 mm. Because of the difficulty of depicting the rectal wall consistently, the thickness of the retrorectal space in the lateral view is given in the following as the shortest distance (in mm) from the rectal lumen to the anterior surface of the 4th sacral vertebra.

Results

Pre-operative Studies

One patient (Case 20) in our series of 23 cases underwent a pre-operative roentgenologic examination at another hospital. Since the rectum was not depicted in the lateral view, only an incomplete evaluation can be made in this case.

Capacity of rectum

The capacity of the rectum was—on a purely subjective basis—evaluated as normal in 10 of 22 cases; in the others it was reduced (Table 1). In three cases (Nos. 2, 4 and 18) the narrowing of the rectum was severe, and was in the nature

TABLE 1.

Case no.	Capacity of rectum	Retrorectal tissue thickness in mm
1	Moderately reduced	12
2	Stricture	17
3	Moderately reduced	15
4	Stricture	32
5	Normal	Normal
6	Slightly reduced	10
7	Normal	Normal
8	Slightly reduced	Normal
9	Normal	Normal
10	Normal	10
11	Moderately reduced	16
12	Normal	Normal
13	Normal	8
14	Normal	Normal
15	Normal	Normal
16	Moderately reduced	20
17	Slightly reduced	Normal
18	Stricture	23
19	Normal	Normal
20	—	—
21	Moderately reduced	11
22	Moderately reduced	13
23	Normal	Normal

of a stricture (Fig. 2). In the remainder, it was slight or moderate.

In 13 cases, repeated roentgenologic examinations of the rectum were made prior to operation. In three of them, the capacity was considered to be normal on the first occasion and subsequently became reduced. In Case 18, the development could be followed until the appearance of stricture.

Mucosal lesions

Inspection of the internal surface of the rectum at roentgenologic examination showed a pathologic relief in 12 cases. It was either finely granulated (Fig. 3) or, in a few cases, inappreciably raised. In the remaining 10 cases the surface was smooth. It should be pointed out, however, that

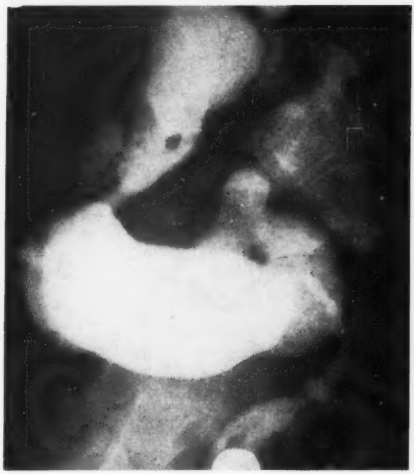


Fig. 2. Lateral view of rectum and sigmoid in a 15-year-old girl (Case 2). Stricture of rectum. The retrorectal space measures 17 mm. Additional strictures are visible in the sigmoid.

proctitis, although mild, was observed at rectoscopy in these cases. The most common finding was an edematous, more or less hyperemic mucosa. In some the mucosa bled easily when touched, but with only one exception no ulcerations were demonstrated. No adenomatous polyps were found.

Retrorectal tissue

Thickening of the retrorectal tissue, the distance from the rectal lumen to the 4th sacral vertebra measuring > 7 mm (range 8–32 mm), was present in 12 cases (Table 1, Figs. 2, 3, 6). In the other 10 cases, the distance was 3–7 mm, and was regarded as ordinary. In six cases, the retrorectal tissue showed a successive increase in thickness when repeated examinations were made in the course of the illness. In a few of them, it had been of ordinary thickness at the first examination. No increase in thickness of the rectal wall was observed.

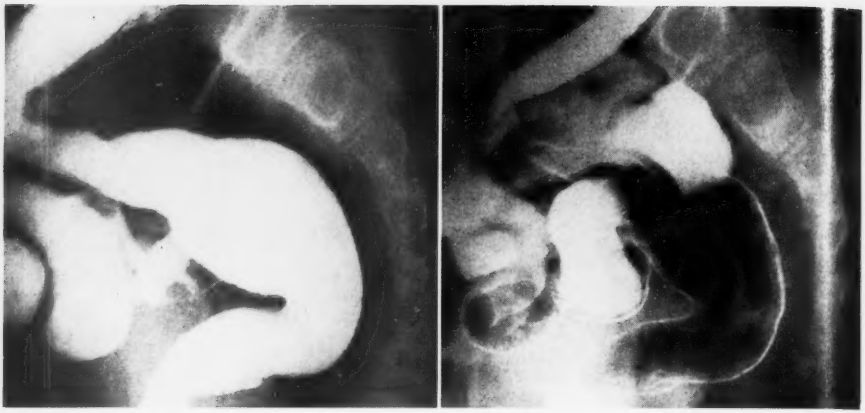


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Fig. 3. Lateral view of rectum and sigmoid in a 14-year-old boy (Case 22). Capacity of lower ampulla of rectum less than normal. Pathologic thickness (13 mm) of retrorectal space. Finely granulated mucosal pattern evident in examination both with barium enema (*a*), and with double contrast medium (*b*). The rectal folds are obliterated.

Kohlrausch's fold

The normal oblique fold in the right segment of the rectum—Kohlrausch's fold—was less distinct in the cases in which the capacity of the rectum was reduced than in those in which it had an ordinary volume. In most cases where narrowing was more than moderate, the fold was obliterated, and when stricture was present it was lacking completely.

Observations at Operation and in Excised Specimens

On excision of the rectum, the adipose tissue behind it was seen to be strikingly voluminous and edematous, and to contain numerous glands. Thus, in Case 22, no less than 50 glands half the size of a pea were present in the excised perirectal tissue. In the cases in which a histologic examination was made, the edema was found to be acellular, and sinus catarrh of the glands was observed. Submucosal fibrosis was marked in Cases 18, 21 and 22. In several cases, excision of the rectum was made more difficult by fibrosis of the perirectal tissue. In the seven cases in which roentgenologic examination showed the rectum to have a normal capacity and the retrorectal space to be of ordinary thickness—a particular note being made of the observations on inspection of the rectum at operation—the serosa had a normal appearance. There were thus no grounds for suspecting the existence of periproctitis in these cases.

Post-operative Studies

Ileorectal anastomosis

In six out of eight cases, which at the time of operation revealed an ordinary capacity and an ordinary distance between rectum and sacrum, the post-operative picture was unchanged. In two (Cases

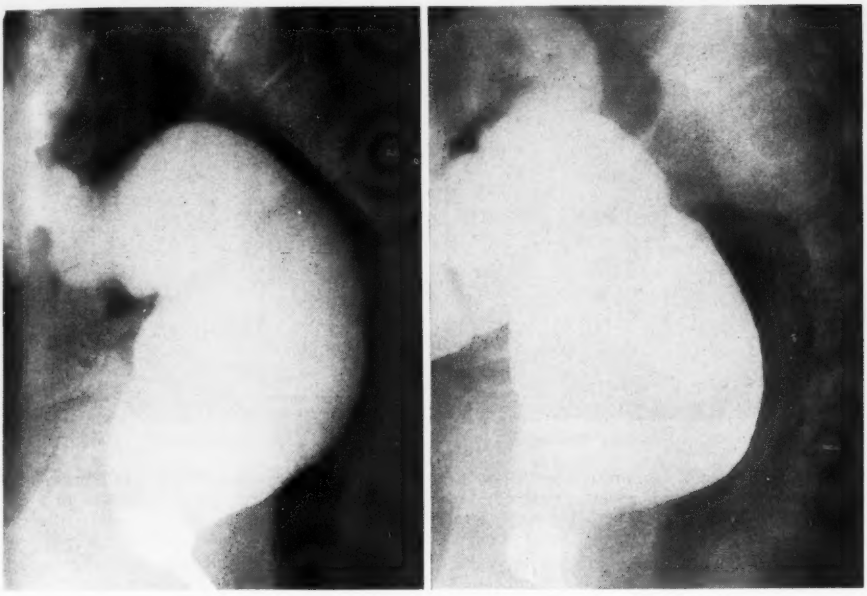

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Fig. 4. Appearance of rectum and retrorectal space in a 14-year-old boy (Case 7), before and after ileorectal anastomosis. (*a*), before operation; (*b*) 1½ years later. Post-operatively, pathologic increase in thickness of retrorectal space (to 20 mm). No alterations in mucosal pattern or distensibility of rectum.

7 and 15), the distensibility of the rectum diminished and a thickening of the retrorectal space developed. Of the remaining two cases (6 and 13), the changes in and around the rectum, present before operation, became even more marked (Figs. 4 and 5).

Isolated rectum

Of the eight cases in which the rectum was isolated and not resected primarily, 3 (Cases 1, 3 and 11) have not been studied post-operatively. No satisfactory roentgen examination was performed before operation in Case 20.

The results in the remaining four cases in which a comparison can be made of the

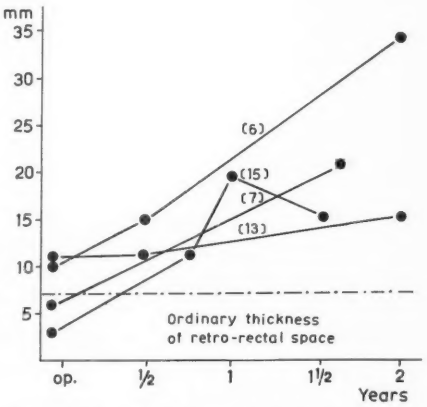
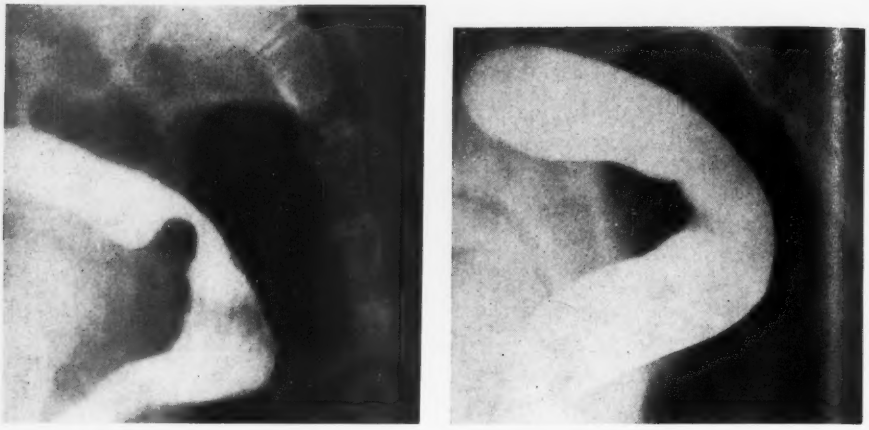


Fig. 5. Pathologic increase in thickness of retrorectal space in four patients after ileorectal anastomosis. Bracketed numerals denote case numbers.



a *b*

Fig. 6. Appearance of rectum in a girl (Case 4): aged 17 years at operation (*a*); and 5 years later (*b*). Capacity of rectum greatly reduced, local stenosis in its upper part. Thickness of retrorectal tissue 32 mm pre-operatively; 18 mm after isolation of rectum. Before operation rectal mucosa granulated. After operation, it is smooth; increase in distensibility of rectum.

findings before and after operation are highly variable.

In Case 10, a slight thickening of the retrorectal space showed complete regression after operation. A favourable effect was also seen in Case 4 (Fig. 6); the abnormal rectum increased its capacity and the retrorectal thickening diminished. Such changes, however, developed in Case 8, in which the rectum had a normal appearance before operation. The abnormal perirectal distance increased in Case 2. Perirectal changes were demonstrated in the post-operative study of Case 20, but no comparison could be made with the conditions present before operation.

The post-operative variations in the thickness of the retrorectal space can be inferred from Fig. 7.

Discussion

It is a general experience that in the majority of cases of ulcerative colitis, the rectum is also involved, so that the condition is actually one of proctocolitis. Many authors are of the opinion that the disease almost invariably has its onset in the rectum, and spreads from this site into the colon (Buie 1925, among others). All large series nevertheless include cases in which the rectum is only inappreciably involved or not at all (e.g. Crohn *et al.* 1947, Manning *et al.* 1955, Watkinson *et al.* 1950).

In none of the 23 cases in the present series could the rectum be regarded as completely healthy. Proctitis was, however, mild from the proctoscopic point of view in eight of them. In these cases, roentgenologic examination showed the rectum to have an ordinary capacity and smooth mucosal surface, and the retrorectal tissue to be of ordinary thickness. In the remaining cases the lesions observed at proctoscopy were more advanced, and were in the form of a glistening, edematous mucosa, infiltrated by ulcerations with or

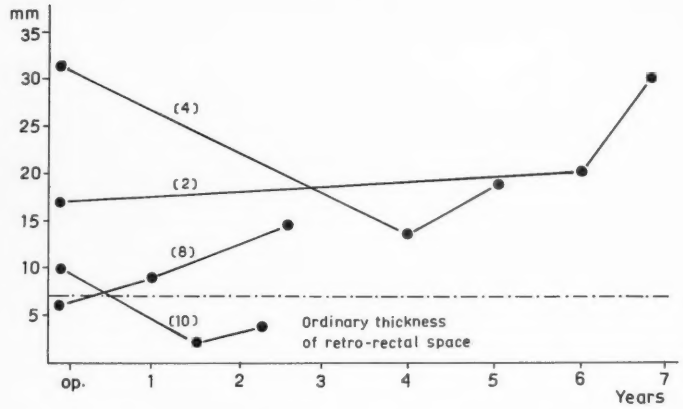


Fig. 7. Variations in thickness of retrorectal space after isolation of rectum in Cases 2, 4, 8 and 10.

without a fibrin coating and granulation tissue. On the roentgenogram, the rectum then had a finely granulated margin. In such cases, the capacity of the rectum was almost consistently reduced, and the distance between rectum and sacrum was pathologically increased.

Roentgenologic examination afforded no evidence of significant thickening of the rectal wall. Consequently, the increased distance from the rectal lumen to the sacrum must be ascribed to an increase in breadth of the retrorectal tissue. This conclusion was confirmed in the seven cases in which the above-mentioned space was thoroughly inspected in connexion with proctectomy. The space was filled by adipose tissue, in which numerous glands were present. Both the glands and adipose tissue were more or less edematous. In a few cases, proctectomy was greatly hampered by marked perirectal fibrosis. Histologic examination confirmed that the retrorectal tissue was the site of an inflammatory process. Despite pronounced thickening of the perirectal tissue in several cases, it retained some plasticity. This was evident from the fact that when the rectum contracted after evacuation of the enema, a further increase took place in the thickness of the retrorectal tissue. Its dimensions remained unaltered only in cases with marked rectal stenosis, and resulting unchanged volume of the rectum after evacuation of its contents.

The influence of the inflammatory process in the rectum on the retrorectal tissue was, in fact, distinct in several cases in which ileorectal anastomosis or isolation of the rectum was performed. Thus, in four of 10 cases in the former group, the distensibility of the rectum diminished, and the perirectal thickening increased; this was reflected in the greater severity of the changes visible at proctoscopy. The cases with an isolated rectum were also characterized by an inverse relation between the capacity of the rectum and thickening of the perirectal tissue. In two of them, a further decrease in distensibility of the

rectum was accompanied by increased displacement of the rectum from the sacrum. Analogously, in the cases in both groups in which the capacity remained normal, no retrorectal thickening developed. When this did appear after isolation of the rectum, it was presumably of the same origin as in all the other cases, and reflected a periproctitis. As far as shrinkage of the rectum is concerned, it is, however, uncertain to what degree the cessation of transport of intestinal contents may have been a contributory factor.

Dick, Berridge & Grayson 1959 (6) stated —in a study of the morphologic basis of the roentgenologically demonstrable changes in the colon in ulcerative colitis— that submucous fibrosis leads to a decrease in intestinal calibre. They nevertheless pointed out that, in this disease, a narrowing of the bowel may occur on other grounds. In the rectum as well, the cause is presumably multifactorial. Although, in every case in our series in which the submucosal fibrosis was particularly studied, the calibre of the rectum was found to be decreased, thickening of the perirectal tissue was a contributory factor. At any rate, in the segment below the peritoneal reflection, the edematous tissue competes for the space in the true pelvis. It can also be mentioned that the complete obliteration of Kohlrausch's fold—which almost invariably accompanies marked narrowing of the rectum—is an additional indication of a deep-lying process in this organ.

Pathologic thickening of the retrorectal space occurs in other conditions as well, and is not specific to ulcerative colitis. Thus, Steinert 1940 (7) described similar roentgenologic features in lymphopathia venerea. Proctitis of other origin—such as the tuberculous or syphilitic form— may be accompanied by thickening and cicatrization of the perirectal tissue (Buie 1960). Virulent spermacystitis in adults may also involve this tissue, with displacement and narrowing of the rectum as a result (10). Abscesses and tumours, as well as sequelae of operations on the true pelvis, are additional causes of widening of the retrorectal space. A large presacral space in patients with Cushing's disease has been observed by Sowerbutts (11).

Levene & Bragg (12) pointed out that, in conditions associated with tension on the mesentery, the rectum cannot be distended normally, and its distance from the sacrum is increased. The shortening of the colon common in our series was never so severe that, *per se*, it affected the distensibility of the rectum. Consequently, on evacuation of the colonic contents, the sigmoid loop was displaced towards the true pelvis in the normal way.

The clinical findings in our series, and the observations made at roentgenologic examination, indicate the following. If the mucosal lesions of the rectum and lower part of the sigmoid are mild, the capacity of the rectum and the thickness of the retrorectal tissue are usually normal. In such cases, in which the roentgenologic features of the rectum are normal, the rectum is likely to be favourably influenced by ileorectal anastomosis after colectomy. This applies, at any rate, to the short-term prognosis. The late prognosis can, on the other hand, presumably be evaluated only after further examinations.

From the roentgenologic point of view, the effect of isolation of the rectum after colectomy was more difficult to assess. This is because roentgenologic examina-

tions were made both pre- and postoperatively in only half of the cases. Progressive shrinkage of the rectum, as well as further increase in thickness of the retrorectal tissue, could not be prevented in two patients, and regression took place in another two.

Summary

A study has been made of the roentgenologic changes in the rectum in 23 patients with ulcerative colitis, aged 4–18 years on their first admission. It is found that the mucosal lesions—which are best assessed at rectoscopy—are not visible as pathologic features on the roentgenogram until they reach an advanced stage. The margin of the rectum is then finely granulated towards the lumen, and the mucosal relief is sometimes raised and irregular. In such cases, the capacity of the rectum is generally reduced. A contributary factor is periproctitis, of which the presence and degree are best established at roentgenologic examination by depicting the rectum in the true lateral view. The distance between rectum and sacrum is then seen to be increased, as an expression of a pathologic process in the retrorectal tissue.

Absence of severe mucosal lesions and of periproctitis, as well as normal capacity of the rectum, are regarded as prognostically favourable with respect to influence on the rectum of ileorectal anastomosis after colectomy.

When pathologic changes of the aforementioned nature are present, the results are found to be less successful. This also applies to the cases in which the rectum has been isolated after colectomy.

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Foetal and Adult Haemoglobin in Newborn Infants with Erythroblastosis Foetalis

by SAM BRODY and LARS ENGSTRÖM

The presence in the blood of the foetus and newborn infant of a special type of haemoglobin, foetal haemoglobin, has long been known (23). This author found considerable differences in the rate of alkali denaturation between foetal haemoglobin and the haemoglobin characteristic of adults. Gradually our knowledge of the physical, chemical and immunological properties of these two types of haemoglobin has increased. A distinction is now possible as regards crystallography (17, 22, 26), X-ray diffraction (36), solubility (22), amino-acid composition (15, 28, 31, 34), antigenic properties (1, 12, 13, 16, 20) and column chromatography (18, 19, 29, 30).

Experimental evidence indicates that adult haemoglobin is already synthesized in the foetus during the first half of pregnancy (2, 35). During the latter part of pregnancy the proportion of this type of haemoglobin in circulating blood is gradually increased. Considerable interest has been devoted to the rate and extent of the change in the proportions of foetal and adult haemoglobin during intra-uterine development, and for references and discussions of the physiological and clinical implications of these and related problems the reader is referred to earlier publications (5, 6, 7, 8, 10, 11).

Several investigators have been interested in the behaviour of the various haemoglobin types in erythroblastosis foetalis. The results vary considerably and from available data it is difficult to form a clear picture of the haemolytic effects on foetal and adult haemoglobin respectively. Jonxis (21) found large amounts of adult haemoglobin in the blood of infants suffering from haemolytic disease of the newborn. Schulman & Smith (32) demonstrated a decrease in the concentration and proportion of foetal haemoglobin in such infants. Ponder & Levine (27), on the other hand, found no differences between a group of infants with haemolytic disease and a control group of normal infants as regards the proportion of foetal haemoglobin.

These controversial results and the various hypotheses based on them point to the necessity of further research in this field. It would seem that reliable conclusions as to possible deviations from the normal in the concentrations or proportions of foetal and adult haemoglobin in erythroblastosis foetalis are possible only

by a thorough analysis of a large case material. The investigations presented to date seem to be based on an insufficient number of patients. Even in a group of normal infants considerable fluctuations in foetal and adult haemoglobin are encountered. Furthermore, the wide differences in the clinical picture of erythroblastosis foetalis introduce a considerable source of variation.

The wide range of the clinical manifestations of the disease, reaching from a symptomless to a fatal course, made it desirable also to analyze a material with reference to the severity of the disease. A classification of erythroblastosis foetalis as mild, intermediate and severe, has been proposed earlier (9) and is employed in the present investigation.

Materials and Methods

In this study 96 newborn infants of mothers with serological evidence of Rh-sensitization were examined. The analyses were performed on cord blood. The blood was collected within a few minutes of birth and before separation of the placenta. Extreme care was taken to avoid contamination with maternal blood.

Thirty-four infants were delivered spontaneously. In 60 cases labour was induced by the administration of oxytocin intravenously. Two patients were delivered by caesarean section (pelvic disproportion). Imminent intra-uterine asphyxia necessitated delivery by forceps in two instances.

The birth-weight of these infants ranged from 2280 to 5350 g. Two infants weighed less than 2500 g and five subjects had a birth-weight of more than 4000 g. No vitamin K was given to the infants included in this study.

All infants had positive results on Coombs' test. The total haemoglobin was determined in the manner described in detail elsewhere (Brody (9). The proportions of foetal and adult haemoglobin were calculated by measuring the rate of alkali denaturation. These determinations were carried out according to the procedure of Betke (3, 4) as modified by Brody (5).

Determination of bilirubin was carried out according to the procedure of Malloy & Evelyn (24) as modified by Ducci & Watson (14).

Nucleated red blood cells were counted on blood smears stained with May-Grünwald and Giemsa solutions. Their number is given per 100 white blood cells.

The clinical severity of the disease varied greatly. Six infants died immediately after birth from erythroblastosis foetalis. Sixty-six subjects were treated with exchange transfusions, varying in number from one to five. The remaining 24 infants required no therapy.

For the elucidation of the relationship between laboratory findings and clinical severity of the disease, the infants were classified in three groups: mild, intermediate and severe. The criteria for this classification have been given earlier and are based on the concentration of free, non-conjugated bilirubin and the number of exchange transfusions required (Brody (9)). The following principles were used:

Group 1 (*Mild*): $\leqslant 15$ mg per cent bilirubin, or $\leqslant 10$ mg per cent after one exchange transfusion.

Group 2 (*Intermediate*): $\geqslant 15$ mg per cent bilirubin, or > 10 but < 15 mg per cent after one exchange transfusion.

Group 3 (*Severe*): $\geqslant 15$ mg per cent after one exchange transfusion, or $\geqslant 10$ mg per cent after two or more transfusions. The infants who died immediately after birth were included in this group.

Statistical analysis was performed according to conventional methods (Snedecor (33)).

Results

The variation in the 96 observations on the cord-haemoglobin levels is graphically

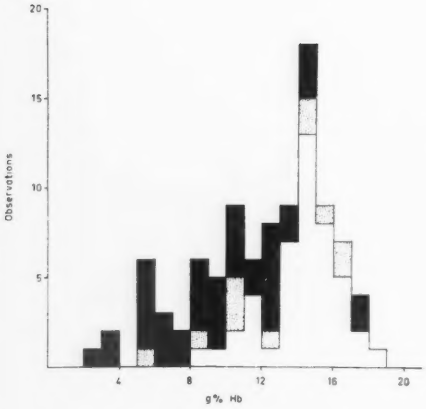

Fig. 1.

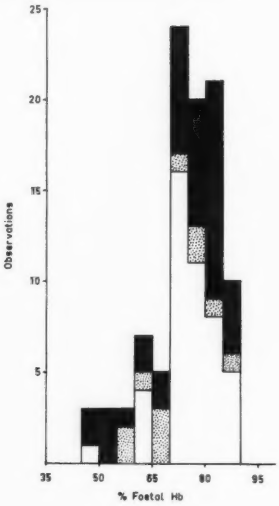

Fig. 2.

Fig. 1. Distribution of cord haemoglobin (total haemoglobin) levels in 96 infants with erythroblastosis foetalis. Infants classified according to the clinical severity of the disease (for criteria of classification, see section on Materials and Methods). White area: mild form of the disease. Dotted area: intermediate form. Black area: severe form.

Fig. 2. Distribution of the proportion of foetal haemoglobin (in per cent of total haemoglobin) in the cord blood of 96 infants with erythroblastosis foetalis. For explanations, see Fig. 1.

represented in Fig. 1. The material has been classified according to the clinical severity of the disease with the criteria given above and the number of observations in each group indicated. As might be expected, low values are predominant in infants suffering from the severe form of the disease.

Fig. 2 shows the distribution of the proportion of foetal haemoglobin in the cord blood. It is expressed as the percentage of total haemoglobin. Differences in distribution as between the various clinical groups is scarcely discernible.

In Figs. 3 & 4 the variation in the concentrations of foetal and adult haemoglobin is shown. In both instances a clear predominance of low values is found in the group of infants suffering from the severe type of the disease.

Table 1 lists the mean values for the concentrations of total, foetal and adult haemoglobin and for the proportion of foetal haemoglobin. These values have been calculated for the entire group of infants with erythroblastosis foetalis as well as for those weighing from 2500 to 3990 g. This has been done to make possible a comparison with the corresponding values for a group of normal infants of the same weight-class. The latter figures are taken from an earlier publication (Brody (7)) and are based on 156 infants. In Table 1 are also summarized the results of calculations on the statistical significance of differences between mean values for the

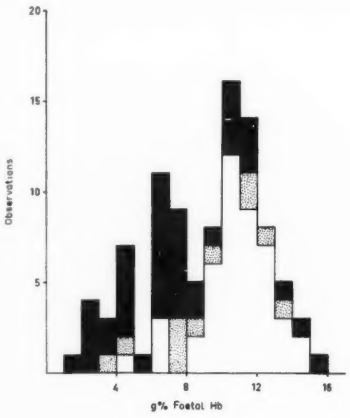

Fig. 3.

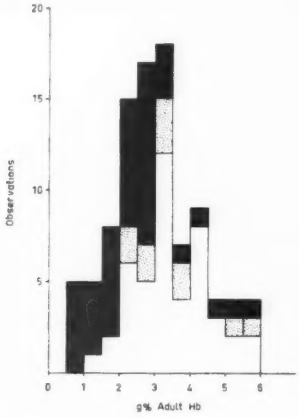

Fig. 4.

Fig. 3. Distribution of foetal haemoglobin levels in the cord blood of 96 infants with erythroblastosis foetalis. For explanations, see Fig. 1.

Fig. 4. Distribution of adult haemoglobin levels in the cord blood of 96 infants with erythroblastosis foetalis. For explanations, see Fig. 1.

various measurements in the group of normal and diseased infants. All differences are statistically highly significant.

In Table 2 the infants with erythroblastosis foetalis have been classified in groups according to the clinical severity of the disease. As may be seen, there is a clear connection between this parameter and the concentrations of total as well as of foetal and adult haemoglobin. A severe course of the affection is accompanied by a decrease in all these respects. On the other hand, the proportion of foetal haemoglobin is approximately constant in all the groups.

The relationship between the concentra-

TABLE 1. *Concentrations of total, foetal, and adult haemoglobin in normal infants and in infants with erythroblastosis foetalis.*

Measurement	Normal infants 2500–3990 g[a] Mean ± S.E.	Erythroblastosis foetalis Entire group Mean ± S.E.	Erythroblastosis foetalis 2500–3990 g Mean ± S.E.	Statistical significance for differences between means (P)[b]
Number of cases	156	96	89	
Total haemoglobin (g/100 ml)	15.81 ± 0.17	12.12 ± 0.38	12.07 ± 0.38	< 0.001
Foetal haemoglobin (g/100 ml)	12.33 ± 0.15	9.11 ± 0.33	9.05 ± 0.34	< 0.001
Adult haemoglobin (g/100 ml)	3.58 ± 0.09	3.01 ± 0.12	3.02 ± 0.13	< 0.001
Foetal haemoglobin (per cent of total haemoglobin)	77.39 ± 0.52	74.14 ± 1.00	73.90 ± 1.13	0.001 < P < 0.01

[a] Values from Brody (7).
[b] Comparison between infants weighing 2500–3990 g.
S.E. = standard error of the mean.

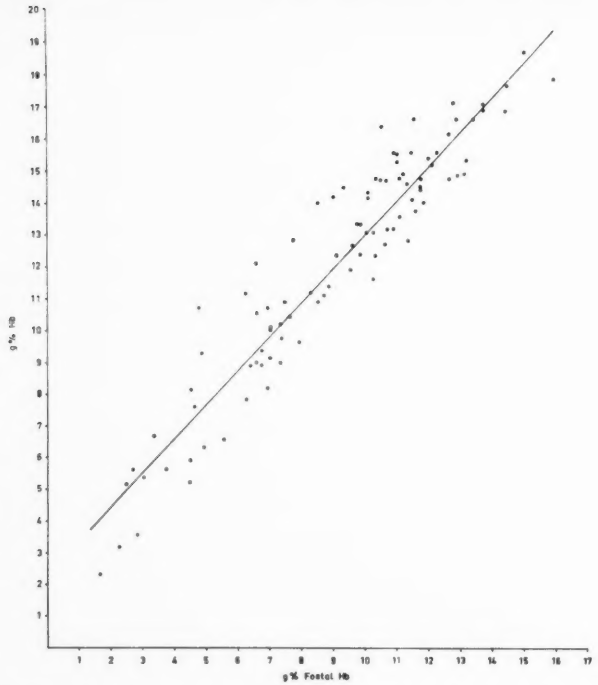

Fig. 5. The relationship between the concentrations of foetal and total haemoglobin in the cord blood of 96 infants with erythroblastosis foetalis. Equation of regression line: $Y = 2.34 + 1.074x$.

tions of foetal and total haemoglobin is graphically demonstrated in Fig. 5. The regression of total haemoglobin on foetal haemoglobin has been calculated and the pertinent statistical data are summarized in Table 3. The correlation is statistically highly significant. Fig. 6 shows the relationship between the levels of adult and

TABLE 2. *Concentrations of total, foetal, and adult haemoglobin in infants with erythroblastosis foetalis classified according to the clinical severity of the disease.*

For criteria of classification, see section on Material and Methods.
S.E. = standard error of the mean.

Measurement	Clinical group 1 (Mean ± S.E.)	Clinical group 2 (Mean ± S.E.)	Clinical group 3 (Mean ± S.E.)
Number of cases	45	11	40
Total haemoglobin (g/100 ml)	14.22 ± 0.31	12.19 ± 1.09	9.74 ± 0.59
Foetal haemoglobin (g/100 ml)	10.77 ± 0.31	8.78 ± 1.01	7.33 ± 0.54
Adult haemoglobin (g/100 ml)	3.46 ± 0.16	3.40 ± 0.36	2.41 ± 0.18
Foetal haemoglobin (per cent of total haemoglobin)	75.45 ± 1.17	70.27 ± 3.04	73.73 ± 1.84

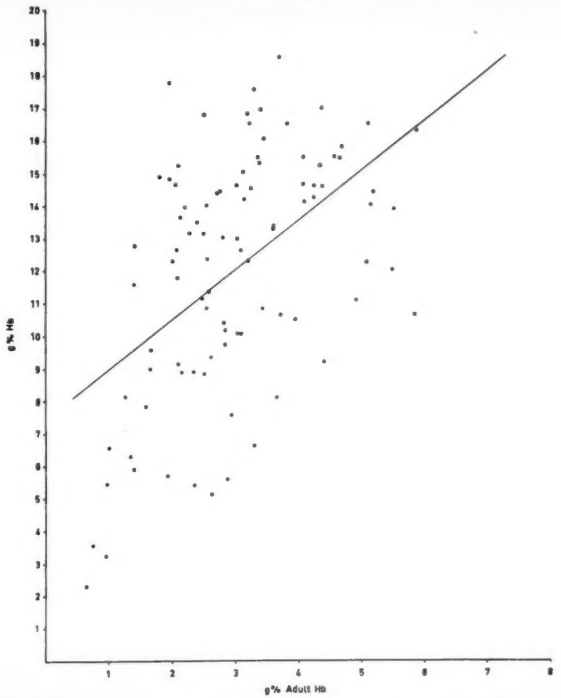

Fig. 6. The relationship between the concentrations of adult and total haemoglobin in the cord blood of 96 infants with erythroblastosis foetalis. Equation of regression line: $Y = 7.50 + 1.535x$.

TABLE 3. *Survey of statistical data.*

The regression of y upon x has been calculated.

	y	x			y	x	
Statistical term	Total haemoglobin (g/100 ml)	Foetal haemoglobin (g/100 ml)	Adult haemoglobin (g/100 ml)	Foetal haemoglobin (per cent of total haemoglobin)	Number of nucleated red blood cells	Total haemoglobin (g/100 ml)	Foetal haemoglobin (per cent of total haemoglobin)
Number of variables	96	96	96	96	86	86	86
Sum	1,163.79	874.5	289.19	7,117.3	6,206	1,066.78	6,344.3
Mean	12.12	9.1094	3.0124	74.1	72.16	12.404	73.7
Sum of squares	15,403.2259	8,974.4908	1009.0213	536,889.83	2,037,108	14,350.3800	480,043.0
Sum of products of x and y		11,683.9977	3717.4100	87,173.985		49,203.78	439,541.3
Variance		1.406	10.32	12.75		10,695	18,588.7
Correlation coefficient (r)		0.948	0.501	0.272		−0.660	−0.1
Regression coefficient (b)		1.074	1.535	0.09674		−24.855	−1.5
Standard error of regression coefficient		0.0373	0.274	0.0371		3.0935	1.2
Significance of regression coefficient (P)		< 0.001	< 0.001	$0.01 < P < 0.02$		< 0.001	$0.2 < P <$

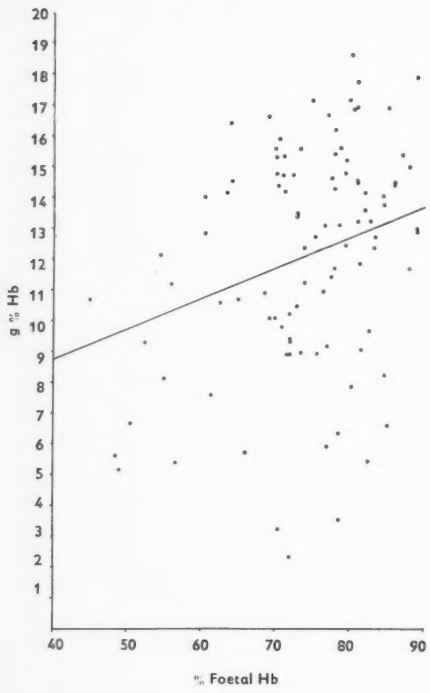

Fig. 7. The relationship between the percentage of foetal haemoglobin and the total haemoglobin concentration in the cord blood of 96 infants with erythroblastosis foetalis. Equation of regression line: $Y = 4.95 + 0.0967x$.

total haemoglobin. Also in this case a highly significant correlation exists (Table 3). Fig. 7 presents the relationship between the percentage of foetal haemoglobin and total haemoglobin. The statistical analysis reveals a significant correlation between these two factors (Table 3).

The number of nucleated red blood cells per 100 white blood cells has been determined in 86 infants. The relationship between the concentration of total haemoglobin and the number of nucleated red blood cells is shown in Fig. 8. The regression of the latter factor on total haemoglobin has been calculated and the correlation is statistically highly significant (Table 3). The relationship between the percentage of foetal haemoglobin and the number of nucleated red blood cells is graphically represented in Fig. 9. Data on statistical analysis are summarized in Table 3. No statistically significant correlation exists between these two factors.

Discussion

The first studies on the proportions of foetal and adult haemoglobin in the blood of newborn infants suffering from erythroblastosis foetalis were made by Jonxis (1948). He found that the diseased infants had a much lower proportion of foetal haemoglobin, and from his observations he concluded that in haemolytic disease of the newborn there is a selective destruction of erythrocytes containing foetal haemoglobin.

This conclusion was at variance with results presented by Mollison (25). By transfusion of Rh-positive adult blood into infants with haemolytic disease this author had demonstrated that there was indiscriminate destruction of the infant's and the donor's cells. The problem was further investigated by Schulman & Smith (32). In agreement with Jonxis (21), they also found a decrease in the mean value of the percentage of foetal haemoglobin in infants suffering from haemolytic disease as compared with the mean value found in normal infants. Some other observations, however, were at varaiance with the conclusion drawn by Jonxis (21). Thus Schulman & Smith (32) found that not only the decrease in the concentration of foetal, but also that of adult haemoglobin, showed

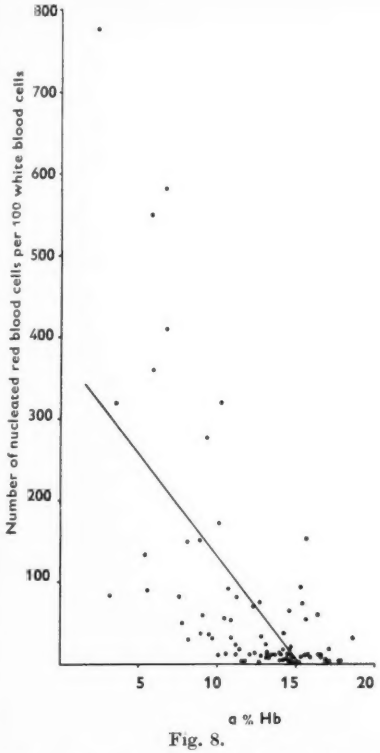

Fig. 8.

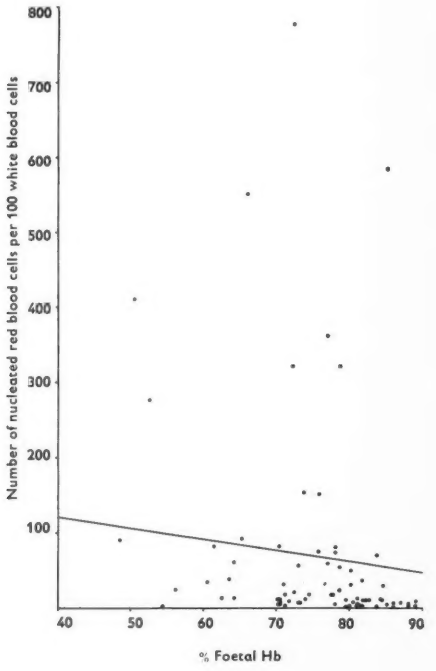

Fig. 9.

Fig. 8. The relationship between the total haemoglobin concentration and the number of nucleated red blood cells in the cord blood of 86 infants with erythroblastosis foetalis. Equation of regression line: $Y = 380.42 - 24.86x$.

Fig. 9. The relationship between the percentage of foetal haemoglobin and the number of nucleated red blood cells in the cord blood of 86 infants with erythroblastosis foetalis. Equation of regression line: $Y = 184.73 - 1.52x$.

good correlation with the decrease of the total haemoglobin concentration. Furthermore, these authors found no correlation between the percentage of foetal haemoglobin and the total haemoglobin concentration.

Schulman & Smith (32) argued that the apparent contradiction between the decrease in the percentage of foetal haemoglobin in infants with erythroblastosis foetalis and the lack of evidence in favour of a selective destruction of foetal haemoglobin might be explained by considering the factor of blood regeneration in response to the haemolytic destruction of the red blood cells. They found that the mean value for the concentration of adult haemoglobin was higher in diseased infants as compared with that found in a group of normal subjects. Classification of the diseased infants in an anaemic and a non-anaemic group revealed that the mean

value for the adult haemoglobin in the former group was not significantly different from that of the normal control group, whereas in the non-anaemic group the amount of adult haemoglobin was significantly higher than normal. In both anaemic and non-anaemic groups, however, the mean values for the concentration of foetal haemoglobin were significantly different from the corresponding figure in the control group. On the basis of these findings Schulman & Smith (32) concluded that their results indicated preferential regeneration of adult haemoglobin in response to haemolysis.

In our material of infants with erythroblastosis foetalis we have found a highly significant decrease in the proportion of foetal haemoglobin as compared with a group of normal infants. This finding is in accordance with that of Jonxis (21) and Schulman & Smith (32). We have also demonstrated a close correlation between the concentrations of foetal as well as adult haemoglobin and the level of total haemoglobin, confirming in this respect the results of Schulman & Smith (32). In contradiction to the findings of these authors, however, our group of diseased infants exhibited a highly significant decrease as regards the concentration of adult haemoglobin (Table 1).

In order to test further the conclusions of Schulman & Smith, we have divided our material into an anaemic and a non-anaemic group, following the same principle as that used by these authors. The line of division (mean normal-haemoglobin minus 2 S.D.) is in our material 11.65 g per 100 ml (Brody (7)). The adult haemoglobin concentration is in our non-anaemic group 3.43 ± 0.14 ($\pm$ standard error of the mean) g per 100 ml, thus not statistically different from that found in a group of normal newborn infants (Table 1). The corresponding figure in our anaemic group is 2.40 ± 0.19 g per 100 ml. The difference from the mean value of the normal control group is statistically highly significant.

Our findings, therefore, do not support the hypothesis of Schulman & Smith of a preferential regeneration of adult haemoglobin in infants with erythroblastosis foetalis. Rather do our data seem to indicate preferential destruction of foetal haemoglobin. There is thus a significant correlation between the total haemoglobin concentration and the percentage of foetal haemoglobin in our material, favouring the hypothesis of Jonxis (21).

We are, however, inclined to modify the view of Jonxis. According to this author, only cells containing foetal haemoglobin are haemolyzed. As has recently been found (Wilton & Brody, to be published), there is in the newborn infant a significant correlation between the diameter of a red blood cell and its relative content of foetal haemoglobin. The larger the cell, the higher its relative content of this type of haemoglobin. It would now seem that the dimensional distribution of erythrocytes in a particular infant will greatly influence the extent of destruction of foetal and adult haemoglobin respectively. As cells with relatively large proportions of foetal haemoglobin dominate the picture in less mature infants, it seems conceivable that the degree of maturity is one factor which might influence the response to the haemolytic process in foetal erythroblastosis as regards the decrease in the proportion of foetal haemoglobin.

It should be mentioned that in spite of

the fact that the concentration of total haemoglobin shows a significant correlation with the percentage of foetal haemoglobin, no such correlation is found for the relationship between this latter factor and the number of nucleated red blood cells per 100 white blood cells (Fig. 9 and Table 3). The degree of anaemia and the number of nucleated red blood cells are only different pathological manifestations of the severity of the disease. However, the percentage of foetal haemoglobin correlates with only one of these factors. Also of interest in this connection is the fact that there is no relation between the clinical severity of the disease as manifested by the degree of jaundice and the requirements for exchange transfusions, and the percentage of foetal haemoglobin (Table 2).

Summary

A study of the total, foetal, and adult haemoglobin levels in the cord blood of 96 infants of Rh-sensitized mothers has been carried out. The distribution of these three factors as well as that of the percentage of foetal haemoglobin is graphically represented. The mean values for the concentrations of total, foetal, and adult haemoglobin and that of the percentage of foetal haemoglobin were significantly lower in this group of infants as compared with normal infants. There was a connection between the clinical severity of the disease and the decrease in the concentrations of total, foetal, and adult haemoglobin. No such relationship was established with the percentage of foetal haemoglobin. The total haemoglobin was significantly correlated with foetal and adult haemoglobin, as well as with the percentage of foetal haemoglobin. The number of nucleated red blood cells was significantly correlated with the total haemoglobin. No such correlation existed between these cells and the percentage of foetal haemoglobin. The results presented here indicate that erythroblastosis foetalis is associated with the preferential destruction of foetal haemoglobin. The extent of such preferential destruction, however, appears to be dependent on the proportion of red blood cells containing high relative amounts of foetal haemoglobin.

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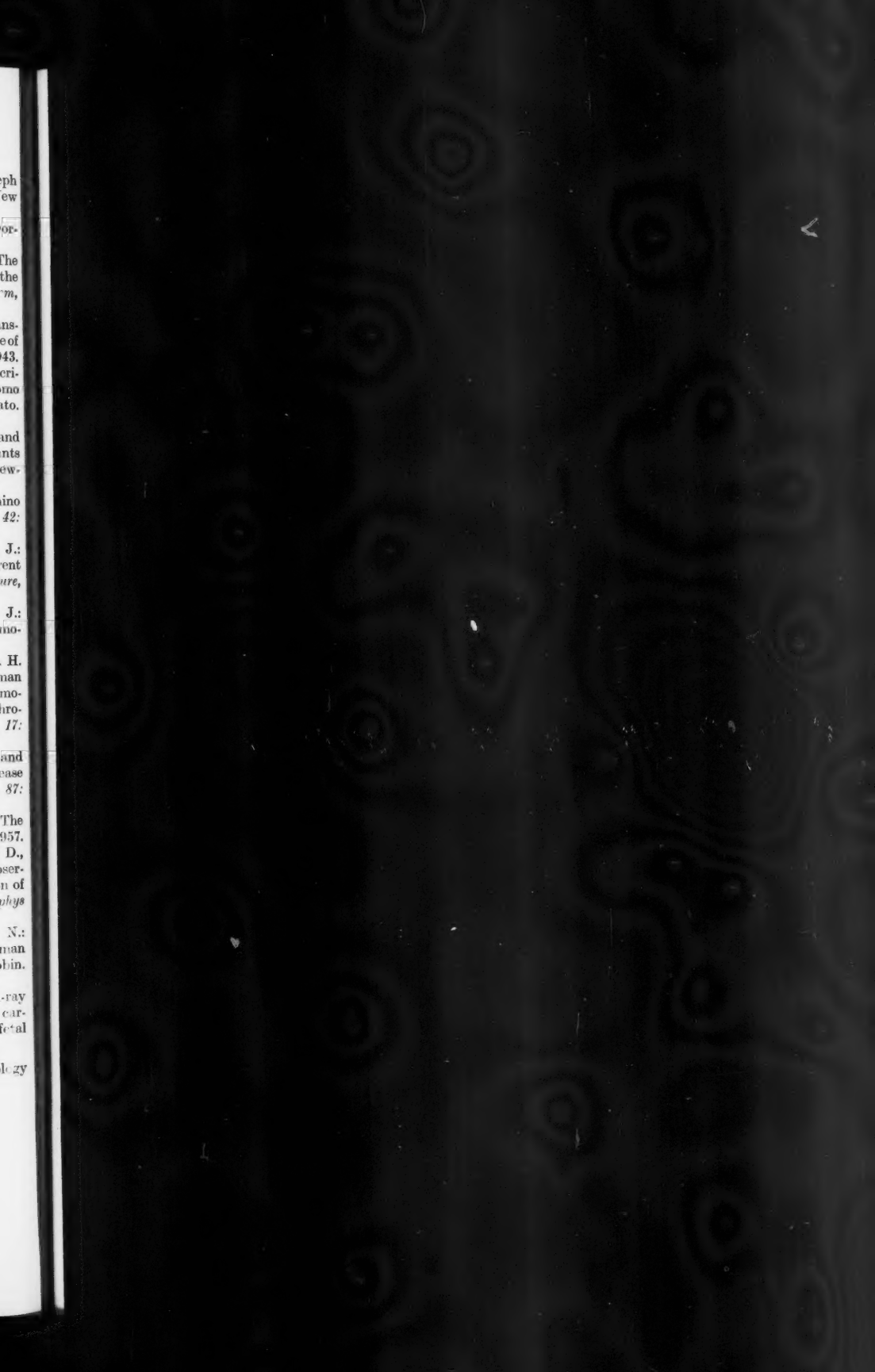

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